Physiological and Functional Alterations after Spaceflight and Bed Rest

AJITKUMAR P. MULAVARA[1], BRIAN T. PETERS[1], CHRIS A. MILLER[1], IGOR S. KOFMAN[1], MILLARD F. RESCHKE[2], LAURA C. TAYLOR[1], EMILY L. LAWRENCE[1], SCOTT J. WOOD[2], STEVEN S. LAURIE[3], STUART M. C. LEE[3], ROXANNE E. BUXTON[4], TIFFANY R. MAY-PHILLIPS[3], MICHAEL B. STENGER[5], LORI L. PLOUTZ-SNYDER[6], JEFFREY W. RYDER[4], ALAN H. FEIVESON[7], and JACOB J. BLOOMBERG[2]

[1]Neurosciences Laboratory, KBRwyle, Houston, TX; [2]Neurosciences Laboratory, NASA-Johnson Space Center, Houston, TX; [3]Cardiovascular and Vision Laboratory, KBRwyle, Houston, TX; [4]Exercise Physiology and Countermeasures Laboratory, KBRwyle, Houston, TX; [5]Cardiovascular and Vision Laboratory, NASA-Johnson Space Center, Houston, TX; [6]School of Kinesiology, University of Michigan, Ann Arbor, MI; and [7]Biostatistics Laboratory, NASA-Johnson Space Center, Houston, TX

ABSTRACT

MULAVARA, A. P., B. T. PETERS, C. A. MILLER, I. S. KOFMAN, M. F. RESCHKE, L. C. TAYLOR, E. L. LAWRENCE, S. J. WOOD, S. S. LAURIE, S. M. C. LEE, R. E. BUXTON, T. R. MAY-PHILLIPS, M. B. STENGER, L. L. PLOUTZ-SNYDER, J. W. RYDER, A. H. FEIVESON, and J. J. BLOOMBERG. Physiological and Functional Alterations after Spaceflight and Bed Rest. *Med. Sci. Sports Exerc.*, Vol. 50, No. 9, pp. 1961–1980, 2018. **Introduction**: Exposure to microgravity causes alterations in multiple physiological systems, potentially impacting the ability of astronauts to perform critical mission tasks. The goal of this study was to determine the effects of spaceflight on functional task performance and to identify the key physiological factors contributing to their deficits. **Methods**: A test battery comprised of seven functional tests and 15 physiological measures was used to investigate the sensorimotor, cardiovascular, and neuromuscular adaptations to spaceflight. Astronauts were tested before and after 6-month spaceflights. Subjects were also tested before and after 70 d of 6° head-down bed rest, a spaceflight analog, to examine the role of axial body unloading on the spaceflight results. These subjects included control and exercise groups to examine the effects of exercise during bed rest. **Results**: Spaceflight subjects showed the greatest decrement in performance during functional tasks that required the greatest demand for dynamic control of postural equilibrium which was paralleled by similar decrements in sensorimotor tests that assessed postural and dynamic gait control. Other changes included reduced lower limb muscle performance and increased HR to maintain blood pressure. Exercise performed during bed rest prevented detrimental change in neuromuscular and cardiovascular function; however, both bed rest groups experienced functional and balance deficits similar to spaceflight subjects. **Conclusion**: Bed rest data indicate that body support unloading experienced during spaceflight contributes to postflight postural control dysfunction. Further, the bed rest results in the exercise group of subjects confirm that resistance and aerobic exercises performed during spaceflight can play an integral role in maintaining neuromuscular and cardiovascular functions, which can help in reducing decrements in functional performance. These results indicate that a countermeasure to mitigate postflight postural control dysfunction is required to maintain functional performance. **Key Words:** FUNCTIONAL TESTS, BODY UNLOADING, EXERCISE COUNTERMEASURES, INTERNATIONAL SPACE STATION, BED REST, SPACEFLIGHT

Physiological responses to microgravity have been studied over the history of human spaceflight. Multiple studies have demonstrated that exposure to spaceflight produces adaptations in sensorimotor, cardiovascular, and neuromuscular systems that are maladaptive upon return to 1*g*. These adaptations are often manifested in balance and gait disturbances (1,2), cardiovascular deconditioning (3,4), and loss of muscle mass, muscle coordination, and strength (5–7). For example, mobile mission tasks after landing on a planetary surface may include a rapid egress from a vehicle. A combination of sensorimotor alterations, reduced muscle strength, or presyncopal symptoms caused by orthostatic intolerance may inhibit timely execution of the egress.

Bed rest is a well-accepted spaceflight analog (8) to understand the implications of muscle disuse (9), cardiovascular deconditioning (10), and to simulate the axial unloading experienced by the sensorimotor system (11). Thus, similar to spaceflight, the effects on human physiology as a result of prolonged exposure to a bed rest environment are multifactorial. Orthostatic intolerance is present after both real and simulated microgravity exposures and is associated with hypovolemia, cardiac remodeling, and decreased systolic and mean arterial blood pressure (12,13). Changes in muscle

Address for correspondence: Jacob J. Bloomberg, Ph.D., Neuroscience Laboratories, Biomedical Research and Environmental Sciences Division, NASA-Johnson Space Center, Mail Code: SK21 Houston, TX 77058; E-mail: jacob.j.bloomberg@nasa.gov.

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properties due to disuse and atrophy can also lead to loss in mobility and contribute to falls as seen in the elderly (14). Further, previous bed rest research focused on sensorimotor alterations suggests that data from prolonged bed rest can be used to help separate modifications within the vestibulospinal system in response to spaceflight from changes in the somatosensory-spinal system driven by axial unloading (11). Therefore, we used the 6° head-down tilt (HDT) bed rest model to investigate and explain these multifactorial effects in isolation from other factors (e.g., isolated environment, vestibular changes, elevated environment CO_2 levels) and compare them with results obtained from spaceflight.

Functional tasks can be part of activities performed inside or outside of a space vehicle in different operational scenarios. Such tasks that are required during operations after landing on a planetary surface or after the return to Earth are generally identified as critical mission tasks. These tasks place varying levels of demands on the functioning of physiological systems. To be able to define an effective and comprehensive countermeasure strategy for preserving performance of functional tasks after prolonged spaceflight, there is a need to understand the contributions of the changes in different physiological systems to the changes observed in functional task performance. To date, no studies have been performed that integrated testing before and after spaceflight with the specific intent to determine how alterations in individual physiological systems impact functional performance of critical exploration mission tasks. Therefore, the goal of this study was to determine the effects of spaceflight on the performance of functional tests that are representative of critical exploration mission tasks and to identify the changes in sensorimotor, cardiovascular, and neuromuscular factors that would likely affect the changes in performance of critical mission tasks. We hypothesize that adaptation to the microgravity environment during long-duration spaceflight will cause changes in cardiovascular, neuromuscular, and sensorimotor function, and these changes will impact the performance of mission critical tasks in a differential manner related to the nature of the task. Ultimately, this information could be used to assess performance risks and inform the design of countermeasures for National Aeronautics and Space Administration (NASA) exploration class missions.

METHODS

Experimental Approach

The experimental approach to meet the goals of this study was to collect functional performance data from International Space Station (ISS) astronauts exposed to the spaceflight environment for a long-duration (>90 d) who performed simulated critical exploration mission tasks and measure a corresponding set of interdisciplinary physiological measures targeting the sensorimotor, cardiovascular, and neuromuscular adaptations known to be affected by spaceflight. The same protocol was conducted on two groups of subjects before and after 70 d of 6° HDT bed rest. The two groups of bed rest subjects were: a control group (BR-C) who did not exercise during bed rest and an exercise group (BR-Ex) participating in the Integrated Resistance and Aerobic Training Study (SPRINT) with an exercise prescription that included aerobic and resistive exercises during bed rest that was similar to that performed by ISS astronauts. Please note that this study was not about testing countermeasures (c.f. 15). The pattern of outcome as a result of bed rest in these two groups of subjects was used to help inform and explain the effects of spaceflight-related deconditioning stemming from prolonged unloading and head-ward fluid shift on functional performance and the effects of a neuromuscular and cardiovascular exercise countermeasure. Combined data from the bedrest and astronaut subjects were then used to develop hypotheses that could explain the relationship between changes in physiological factors and corresponding changes in these functional tasks.

Subjects

Thirteen astronauts (11 men, 2 women; age, 47 ± 5 yr; height, 178 ± 6 cm; body mass, 84 ± 14 kg; mean ± SD) taking part in long-duration missions aboard the ISS with an average duration of 159 d (±17 d) volunteered to participate in this study. In addition, 10 subjects in the BR-C group (10 men; age, 38 ± 7 yr; height, 175 ± 6 cm; body mass, 80 ± 9 kg), and nine subjects in the BR-Ex group (9 men; age, 34 ± 6 yr; height, 178 ± 4 cm; body mass, 77 ± 7 kg) volunteered to participate in 70 d of 6° HDT bed rest. All bed rest participants had to pass the NASA Class III physicals before being accepted as subjects for this study. The protocols were approved by the institutional review boards for NASA Johnson Space Center (NASA-JSC) and the University of Texas Medical Branch in Galveston, TX. All subjects gave informed consent before participating in the study.

Sessions

All testing was performed at NASA-JSC. Table 1 shows the average (range) session day(s) before (pre) and after (post) either spaceflight or bedrest (spaceflight, 3 pre and post; bed rest, 3 pre and 4 post sessions) across each groups

TABLE 1. Average number of days (range) when test sessions were completed before spaceflight or the beginning of bed rest (pre mission), or after spaceflight or the end of bed rest (post mission).

		ISS	Bed Rest Control	Bed Rest Exercise
Pre mission	Session 1	108 (285–70)	7 (8–5)	8 (11–6)
	Session 2	59 (78–39)	3 (0)	3 (6–3)
Post mission	Session 3	1 (0)	0 (0)	0 (0)
	Session 4	8 (6–9)	1 (0)	1 (0)
	Session 5	37 (28–54)	6 (6–7)	7 (5–9)
	Session 6	N/A	11 (10–13)	12 (10–13)

of subjects when testing was performed. The ISS astronauts were tested approximately 1 d after landing; they traveled by NASA aircraft for ~24 h from the landing site in Kazakhstan to Houston, TX. In contrast, bed rest subjects were tested just after rising on the last day of bed rest (with the exception of the Plasma Volume Test which was performed just before rising). The first session before both spaceflight or bed rest, and hence for all groups, was regarded as a familiarization session, and resulting data were not analyzed and hence neither used nor reported in this paper. Subjects were transported from the Flight Analogs Research Unit (FARU) at the University of Texas Medical Branch in Galveston, TX to NASA-JSC for all testing sessions during the pre and post bed rest periods. During transportation for post bed rest testing, subjects remained in the 6° HDT posture on a gurney in a specially equipped van. For the first post bed rest testing, subjects were instrumented while still supine before standing up and performing the test protocol for this study which were the first activities the subjects performed immediately upon standing up after 70 d of bed rest.

Bed Rest Protocol

Bed rest subjects resided at the FARU. Details of the standardized bed rest protocols have been described in this issue of the journal including among other details subject selection criteria, details of diet, and exercise protocols (16). During bed rest, all subjects performed supervised, in-bed stretching exercises twice daily and were permitted to prop themselves up on their elbow while eating meals, but were not allowed any weight-bearing activity beyond the testing and exercise sessions included in the study.

Bed Rest Exercise Protocols

Exercise protocols were performed horizontally for logistical purposes as detailed in a companion paper (15). The BR-Ex subjects followed the SPRINT exercise prescription, 6 d·wk^{-1}. Continuous cycle ergometer exercises were conducted on a Lode® supine cycle ergometer on the same day as resistance exercises. Resistance exercises performed using a custom built horizontal squat machine and treadmill interval exercises performed on a vertical treadmill (Standalone Zero-Gravity Locomotion Simulator, subjects targeted to be loaded from 75%–80% body weight) were conducted on alternate days. Brief details of the SPRINT exercise prescription is provided as supplemental content (see Table, Supplemental Digital Content 1, Bed rest exercise protocol, http://links.lww.com/MSS/B251).

Astronaut Exercise Protocols

Loehr et al. (17) have outlined the ISS crewmember exercise protocols that were developed and implemented on an individual basis in accordance with their crew surgeon and an Astronaut Strength, Conditioning, and Rehabilitation specialist. Briefly, inflight crew time was made available to each crewmember 6 d·wk^{-1} for 90 min of resistance exercise and 60 min of cardiovascular exercise daily (time includes preparation, hardware configuration, and hygiene). Resistance exercises were performed on the Advanced Resistive Exercise Device (ARED) and typically involved upper-body (e.g., upright row, bent over row/bicep curl) and lower-body (e.g., squat, dead-lift, and heel raise) exercises. Cardiovascular exercise involved continuous or interval exercise using a cycle ergometer or a treadmill. For treadmill exercise, astronauts donned a harness and loaded in the range from 58% to 85% BW using bungees according to an individual prescription to keep them in contact with the motorized treadmill and provide a ground reaction force (GRF) at their feet.

Functional Tests

For each subject, the study protocol included seven functional tests. Inputs from a number of different NASA operational organizations were gathered to inform and identify the most demanding critical mission tasks required immediately during operations on a planetary surface and after the return to Earth. Activities the crew would be expected to perform in the first few hours/days after landing on a planetary surface or after the return to Earth that were considered critical to landing, setting up the hab, crew safety are generally identified as critical mission tasks. Task analyses of these critical mission tasks yielded a set of generic functional elements that were implemented as a set of Functional Tests in this protocol to evaluate the ability of subjects to perform challenging tasks that could be part of activities performed inside or outside of a space vehicle in different operational scenarios (see Table, Supplemental Digital Content 2, relationship between critical mission tasks and functional tests, http://links.lww.com/MSS/B252).

Seat Egress and Walk Test. The Seat Egress and Walk Test (Fig. 1A) enabled the measurement of the ability to rise from a seated position and walk while avoiding obstacles to test mobility (2). In this test, subjects were seated on a custom-built chair and strapped in with a five-point harness with a single-release buckle. At the sound of a tone, subjects released the harness by turning the buckle, stood up from the chair and then completed the obstacle course. Subjects were instructed to complete the course as quickly and as safely as possible without touching any obstacles. The primary performance metric was time to complete the entire obstacle course (Completion Time, s).

Recovery from Fall/Stand Test. The Recovery from Fall/Stand Test (Fig. 1B) measured the ability to maintain postural control after standing up from a prone position and has been previously used to evaluate the functional impact of variation in spacesuit designs, as well as being one of the strongest independent risk factors associated with fall related injuries (18). In this test, subjects rested in a prone position on a foam mat for 2 min, then stood up as quickly as possible onto a force plate (Kistler, model 9286A, Kistler Instruments, Winterthur, Switzerland) when signaled by the sound of a tone, and maintained a quiet standing position for 3.5 min. In the upright stance, subjects were instructed to

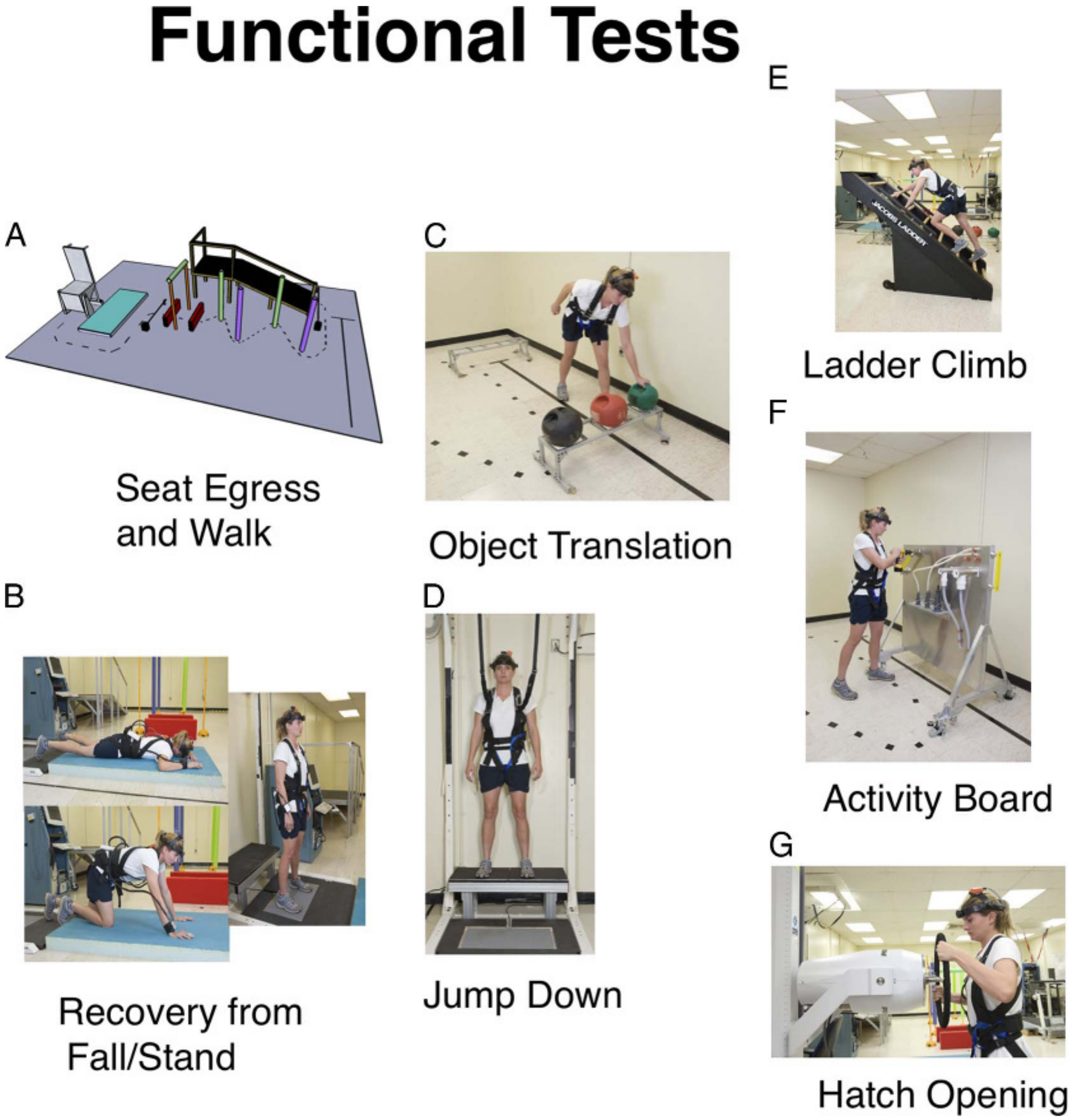

FIGURE 1—Functional tests used in this study included: (A) Seat Egress and Walk, (B) Recovery from Fall/Stand, (C) Object Translation, (D) Jump Down, (E) Ladder Climb, (F) Activity Board, (G) Hatch Opening.

stand comfortably with their feet approximately shoulder-width apart, with eyes forward, and to refrain from talking except to report symptoms for 3.5 min after the tone sounded. Data were acquired from the force plate at 500 Hz. Center of pressure (COP) coordinates were calculated from the GRF collected. The primary performance metric was mean sway speed (MSS, $cm \cdot s^{-1}$). The MSS was defined as the average rate of the resultant (2D) COP displacement calculated over the final 3 min of the standing period. The MSS measured the ability of the postural control system to maintain upright stance while recovering from a prone posture that also induces an additional orthostatic challenge.

Object Translation Test. The Object Translation Test (Fig. 1C) measured the ability to pick up and move objects (tools, equipment, rock samples) from one location to another. In this test, subjects transferred three weights with handles (2.7, 4.5, 9 kg; CorBall, Power Systems Inc., Knoxville, TN) one at a time from least heavy to most heavy, a distance of 2.4 m and placed them in a receptacle (26 cm in height) and then transferred the weights back to the initial receptacle in the same order. All weights were equipped with grip handles. The primary performance metric was time to complete the entire task (Completion Time, s).

Jump Down Test. The Jump Down Test (Fig. 1D) evaluated the ability of crewmembers to jump down from landing vehicles, habitats and during ambulation on uneven terrain during exploratory activities. Upon hearing a tone that began the trial, subjects performed a two-footed hop off a platform from a height of 30 cm onto a force plate that measured the GRF, returned to a standing position and remained still with the arms at their sides until the end of the trial. The trial ended 10 s after the sound of the tone. Three jump trials were performed per session; however, only the results of the first trial are reported here. Force plate data were collected at 4000 Hz. The GRF components were filtered using a second-order low-pass Butterworth filter with cutoff frequency of 10 Hz. The primary performance metric was Postural Settling Time, which quantifies the time taken by the postural control system to recover from a jump-induced perturbation. Postural Settling Time was defined as the time elapsed between touchdown and the first instance when the resultant shear GRF component remained within three standard deviations of the mean of the corresponding GRF during the quiet stance for a minimum duration of half a second. Quiet stance period was defined as a 2-s period of least variability of the resultant shear GRF component within the last 4 s of the trial. The mean and standard deviation of this period of quiet stance was used to calculate the Postural Settling Time (s).

Ladder Climb Test. The Ladder Climb Test (Fig. 1E) simulated and tested the ability to ingress a planetary landing vehicle or habitat. In this test, subjects climbed a passive treadmill ladder (Jacobs Ladder, LLC, North Tonawanda, NY) at a self-selected pace until they completed 40 rungs. Subjects were told to perform the task as quickly and as safely as possible. The primary performance metric was time to completion (Completion Time, s).

Activity Board Test. The Activity Board Test (Fig. 1F) measured crewmembers' ability to perform manual assembly and repair tasks while standing. The manual assembly and repair tasks included: 1) moving two hose connectors from their initial attachments to an adjacent attachment, 2) moving three electrical-connectors from vertical positions to horizontal positions, and 3) removing and installing a handle using a cordless power driver to loosen two screws that locked the handle into C-channels at each end. The primary performance metric was time to complete the entire set of subtasks (Completion Time, s).

Hatch Opening Test. The Hatch Opening Test (Fig. 1G) simulated a spacecraft or habitat hatch-opening task. For this evaluation, the rotation of a 22.86-cm-radius handle wheel attachment on a PrimusRS System (Baltimore Therapeutic Equipment Technologies, Hanover, MD) was fixed. Subjects were instructed to, while standing, turn the wheel counterclockwise for 3 to 5 s with increasing torque up to their maximum effort. The PrimusRS recorded the torques during each session at 1000 Hz. The primary performance metric was peak force produced on the wheel during the test (Force, N).

Physiological Tests

For each subject, the study protocol included 15 physiological tests designed to assess sensorimotor, cardiovascular and neuromuscular function alterations associated with exposure to spaceflight. The primary purpose of the physiological tests was to determine if changes in measures of sensorimotor, cardiovascular, and neuromuscular performance were related to and may contribute to changes in functional test outcomes.

Plasma Volume Test. Plasma volume was measured using a modified carbon monoxide rebreathing method (19). Blood samples from this test were analyzed by the NASA-JSC Clinical Laboratory (College of American Pathologists accredited) for hematocrit, hemoglobin, and carboxyhemoglobin. Hemoglobin and hematocrit were measured using the Coulter LH750 (Beckman Coulter, Inc., Brea, CA). Carboxyhemoglobin was analyzed using the IL 682 co-oximeter (Instrumentation Laboratory Company, Bedford, MA). From these values, plasma volume (volume, L) was calculated.

HR and blood pressure during the Recovery from Fall/Stand Test. The Recovery from Fall/Stand Test as described above was also used to acquire cardiovascular system parameters by collecting electrocardiogram and blood pressure data continuously throughout the test. Previous data collected in astronauts returning from long-duration missions suggested that the earliest signs of presyncope in orthostatically intolerant astronauts ($n = 5$) did not occur until 5.5 min into a passive head-up tilt test (3). Hence, a 3.5-min operational version of the stand test used in an earlier investigation (20) was used to standardize a submaximal stressor of the cardiovascular system while (a) minimizing the risk of subjects developing presyncopal symptoms, (b) meeting testing time requirements, and (c) ensuring the ability for subjects to complete the remainder of the study.

HR was measured from the high fidelity 12-lead electrocardiogram data (Mortara Instruments, Milwaukee, WI) which were collected at 1 kHz and saved to flash memory for offline analysis of HR. The continuous blood pressure waveform data acquired using a Portapres (TNO Medical, The Netherlands) ambulatory blood pressure monitor were saved to a flash drive at 200 Hz and processed offline to estimate the systolic and diastolic blood pressure. The arterial blood pressure measured was corrected to brachial artery pressure using a hydrostatic adjustment level with the heart. Mean arterial pressure (MAP) was calculated as the sum of 1/3 systolic arterial pressure and 2/3 diastolic arterial pressure. HR and MAP were averaged during the 2 min of prone period and the last 3 min of standing and were used for computing the changes from prone to standing periods. This ensured that artifacts resulting from the act of standing and the settling phase were removed from the analyses. The Change in Heart Rate (bpm) and Change in MAP (mm Hg) were the cardiovascular physiological parameters used to quantify the orthostatic stressor induced as a result of the subjects' change in body orientation from prone to upright posture.

Neuromuscular Drive. In this study, the twitch interpolation method was used to assess neuromuscular drive during knee extensions and details of the test in this study have been described previously (21). In this test, subjects sat in a modified knee extension device (NT-1220; Nautilus, Inc., Vancouver, WA) equipped with a load cell (Transducer Techniques, Temecula, CA) and customized for isometric strength testing. Testing was performed at a knee angle of

70° and hip angle of 85°. Force data from the load cell were sampled at 5000 Hz and low pass filtered at 220 Hz. Surface electrodes (7.5 × 13 cm, ValuTrode; Axelgaard, Fallbrook, CA) were placed on the proximal and distal portions over the quadriceps muscle. A stimulator (Digitimer DS7AH, Welwyn Garden City, UK) was used to deliver a supramaximal doublet pulse sequence at 100 Hz with a 200-μs pulse width at an amplitude determined during each session to the quadriceps muscle during the plateau phase of the maximum voluntary contraction (MVC) approximately 2 s into the contraction and within 1–2 s after MVC. This test was repeated three times. The increase in force after the doublet (twitch force during MVC) as well as after the MVC (potentiated twitch) were measured. The central activation capacity was calculated as [1 − (incremental twitch force during MVC/potentiated twitch force)] × 100. The primary dependent variable in this test was the maximum value across the three trials for the calculated central muscle activation capacity (Activation Capacity, %).

Upper- and Lower-Body Isometric Strength Tests. Details of this test for the lower and upper bodies have been described previously (21). Isometric strength of the lower body was measured using supine bilateral leg press testing. This was performed using a customized 35° leg press machine (6000a Leg Press; Nebula Fitness Equipment, Versailles, OH) equipped with a force plate attached to the foot plate. During this test, the foot plate position was fixed such that the subject's knee angle was 90°. Bilateral leg press isometric force was measured by the force plate during a leg press MVC. For the upper body, subjects first lay supine on a bench inside a safety cage specifically-designed to measure muscle power (FT700 Power Cage; Fitness Technology, Skye, SA, Australia). Isometric bench press strength for the upper body was performed in the supine position with the bar fixed by mechanical stops as close to subjects' chest as possible with bar height and hand position standardized within subjects for all sessions. Isometric force for the upper body was measured by a force plate under the bench during a bench press MVC. For both tests, subjects performed three maximal efforts with no countermovement for 5 s with 30 s of rest in between. Subjects were instructed to reach maximal effort as quickly as possible. Force data were collected at 1000 Hz and low-pass filtered at 4 Hz. The primary dependent variable in both these tests was the maximum isometric force (MIF, N) value produced across the three repetitions. Strength was measured isometrically because of the efficiency, reliability, and inherent safety associated with this method (21).

Upper- and Lower-Body Isotonic Power Endurance Tests. Details of this test for the lower and upper bodies have been described previously (21). Dynamic lower-body power and endurance (work) were measured in a single test using a ballistic, concentric-only bilateral leg press (initial knee angle of 90°) on the same leg press machine used to measure the lower-body MIF. Subjects were instructed to extend their legs through a full range of motion, pushing the load as forcefully and quickly as possible through 21 consecutive repetitions. The external load was set at 40% of the measured lower-body MIF to maximize mechanical power. Dynamic upper-body power and endurance were measured by having the subjects perform 21 ballistic, concentric-only bench press movements using a load set at 30% upper-body MIF to maximize mechanical power on the same bench press machine used to measure the upper-body MIF. Subjects began the upper-body muscle power endurance test with the bar resting on mechanical stops above their chest. Subjects were instructed to extend their arms through a full range of motion while pushing the load away from their chest as forcefully and quickly as possible. For both tests, a magnetic brake (Fitness Technology) was engaged when the load in each test reached peak height, allowing test operators to easily and rapidly return the weight to the starting position so that subjects did not perform eccentric muscle actions. The potential limitation of reduction in blood flow to muscles, in this protocol to estimate dynamic lower-body power and endurance, was minimized by the relaxation of muscles between consecutive concentric muscle action. An inline position transducer measured the excursion of each weight throw. Force and position data were sampled at 300 Hz and low-pass filtered at 4 Hz. The value of the primary dependent measure of power reported was the peak value achieved during any of the 21 attempts—typically that occurred within the first three repetitions (Maximum Power, W). The cumulative total amount of work performed during the entire 21 repetition test was used as a primary dependent measure of endurance (Total Work, J).

Dynamic Posturography Test. Postural stability was assessed using one of the Sensory Organization Test conditions provided by EquiTest System platform (NeuroCom, Clackamas, OR) and has been used in previous studies (1,22,23). During testing, subjects were instructed to maintain stable upright posture for 20-s trials with feet positioned shoulder width apart on a force plate, eyes closed, and arms folded across the chest. Three trials were conducted with eyes closed to disrupt vision and with a sway-referenced support surface in the anterior–posterior (AP) direction intended to disrupt somatosensory feedback. This test was modified to increase its sensitivity by requiring subjects during this test to pitch their heads ±20° at 0.33 Hz as cued by an oscillating tone provided over headphones (1). Inertial sensors (Xbus Kit; Xsens Technologies B.V., Enschede, The Netherlands) mounted on the headphones were used to quantify head position. Trials during which subjects were unable to perform the head movements appropriately (defined as two standard deviations from the mean for either amplitude or frequency) were removed. Trials were terminated if subjects moved their feet, began to take a step, or raised their arms. The COP was calculated from the data obtained from the force plate sampled at 100 Hz and then filtered to estimate center of mass (COM). The subject's sway angle was then derived from the COM that was assumed to be above the support surface at approximately

55% of total subject height (SMART EquiTest System Operator's Manual, NeuroCom International). The AP peak-to-peak sway angle of the COM was used to compute a continuous equilibrium (cEQ) Score scaled relative to a maximum theoretical peak-to-peak sway of 12.5° and further normalized by the percent time of the trial completed (24). The primary dependent variable in this assessment was the median of the cEQ Score across the three trails as reported previously.

Tandem Walk Test. The purpose of the Tandem Walk Test was to assess changes in dynamic balance control (25). In this test, subjects walked in a heel-to-toe fashion at a self-selected speed for 10 steps per trial with their arms crossed on their chest and their eyes closed. Three trials were performed per session, and the video of each trial was recorded. Three reviewers examined the videos independently to determine the number of correct steps during each trial. A "misstep" was defined as any of the following: (a) the subject's stepping foot crossing over the plant foot; (b) the subject stepping to the side before completing the step; (c) the subject's stepping foot swinging in a wide, arcing path before stepping down; (d) a step duration greater than 3 s; or (e) an excessive gap between the heel of the front foot and toe of the back foot when the step was completed. Videos for all trials across all sessions for a given subject were pooled, then the order was randomized to minimize reviewer bias based on their awareness of the session. After all reviewers completed their assessments, the median value was used to determine the percentage of correct steps for that trial. The primary dependent variable in this assessment was the average percentage of correct steps across the three trials (Percent Correct Steps, %).

Fine Motor Control Test. The Grooved Pegboard Test (Lafayette Instrument Company, Lafayette, IN), a common test for neurological and vocational assessment of fine motor control (26) that has been used for monitoring recovery post brain injury (27,28) as well as after cardiopulmonary surgical procedures (29), was used for this assessment. Subjects were required to rotate pegs with a ridge along one side to match the slot position in a keyed hole before they could be inserted. While seated in a chair, subjects were asked to use their preferred hand to pick up the pegs one at a time and place them in the holes in a predetermined order that was kept consistent across sessions. Subjects completed 25 holes with randomly positioned slots for each session. The primary performance metric was time to complete the entire board (Completion Time, s).

Force Control Test. Details of this test for the lower and upper bodies have been described previously (21). Lower-body force control was measured by asking the subjects to exert a fixed isometric force on the knee extension bar in the same configuration as described above in the Neuromuscular Drive Test with the same knee and hip angles. For the upper body, force control was measured by asking the subjects to exert a fixed isometric force using the bench press device in the configuration used for the Upper-Body Isometric Strength Test described above. Subjects performed two trials, each 30 s in duration, with 30 s of rest in between. In each trial subjects received visual feedback from a computer display to which they attempted to match their force output with a reference line indicating the targeted force output, which was 5% of their pre-flight or pre-bed rest MIF for the first 15 s and then the visual feedback was turned off for the last 15 s. During the last 15 s period of the trial, subjects did not receive any visual or verbal feedback and were required to perform the remainder of the test based upon perception of effort alone. The primary dependent variable in this test was the lowest coefficient of variation (CV) across the two trials during the middle 10 s no-visual-feedback period for both the lower-body and upper-body tests (Force Control, CV).

Statistical Analysis

Effects of spaceflight and bed rest on functional and physiological tests. Using only the two pre- and the first post-"mission" (spaceflight or bed rest) observations, we used a mixed-effects regression model (30) to estimate and test the degree of change (pre- to post-mission) on each functional test and physiological outcome measure for each subject group. This enabled us to visualize the pattern of changes in functional test performance and physiological measures as a result of exposure to spaceflight and bed rest (with and without exercise countermeasures). For many of these outcomes, original data were transformed to meet mixed-model assumptions of normality of residuals and random effects (see Table, Supplemental Digital Content 3, transformations performed on the variables to satisfy mixed-model assumptions, http://links.lww.com/MSS/B253). Estimates and 95% confidence limits for the mean change in the transformed metric were then converted to estimates and 95% confidence limits for the change in median in the original metric through back-transformation (31). Although we expected that the medians likely would decrease with spaceflight or bed rest for most outcomes, to be conservative we reported two-sided P values for each test.

Mapping the relationship between changes in functional and physiological test outcomes. One of the goals of this study was to identify physiological systems whose change after long-duration spaceflight or bed rest would likely affect changes in performance outcomes of one or more of the functional tests. To do this, we used the Somers' D statistic (32) to quantify the degree of association between session-to-session changes in each physiological measure with corresponding changes in performance for each of the functional test measures. P values for testing the null hypothesis $D = 0$, were calculated using the methods described in (32). See Supplemental Digital Content 4, calculation of Somers D, http://links.lww.com/MSS/B254.

Adjustment for multiplicity. For each of 22 outcome measures (15 physiological + 7 functional test), mixed-model regression was used to compare pre-post changes for each of 3 subject groups (Figs. 2–5). As a result, the total number of tests of this type was 22 × 3 = 66. Furthermore, tests of significant association between changes in each physiological measure (n = 15) with each functional measure (n = 7) resulted in 105 = 15 × 7 values of Somers D and associated P-values. Therefore, instead of the nominal value of 0.05, we used smaller P value thresholds for flagging significant results: 0.008 for the mixed-model-based tests and 0.003 for the Somers' D–based tests. These thresholds were chosen to control the false discovery rate (FDR) to 1% using the method of Benjamini et al. (33). The FDR is the expected percentage of "discoveries" (i.e., "significant" findings) that are in fact, spurious.

RESULTS

Effects of Spaceflight and Bed Rest on Functional and Physiological Tests

Estimated medians (±95% CI) across the two pre sessions and the first post session by subject group (ISS, BR-C, and BR-Ex) are shown in Figure 2 for the functional test outcomes and for the three types of physiological test outcomes in Figures 3–5. Significant changes (P < 0.008) from pre to post sessions are indicated with a star symbol (⋆). Actual P values for each comparison are shown in Table 2. Significant findings are highlighted in red to allow the reader to make visual comparisons on a macro level comparing the findings of pre to post differences for each of the ISS, BR-C, and BR-Ex subject groups for the functional and physiological outcomes. In addition, we have also chosen to highlight the difference with P-values close to the threshold ($0.008 \leq P \leq 0.009$) in pink.

For the functional test outcomes (top section, Table 2, Figure 2), we observed a significant increase in median Completion Time for the Seat Egress and Walk Test as well as for MSS in the Recovery from Fall/Stand Test for all three subject groups. For the Object Translation and Jump Down tests, performance was also significantly degraded for ISS and BR-C subjects, but there were notable exceptions in the BR-Ex group who showed no significant change in performance for either of these tests. For the BR-C group, although the increase in median Postural Settling Time for the Jump Down Test was statistically significant after bed rest, subjects showed comparatively reduced changes relative to ISS subjects. Both bed rest groups showed a significant increase in Completion Time in the Ladder Climb Test, whereas the ISS subjects showed marginal significant increase in Completion Time (P = 0.009). Performance on the Activity Board and Hatch Opening tests was not noticeably changed after spaceflight or bed rest. Hence, in general, as reflected in Table 2, functional tests with greater demand for postural control during quiet stance and walking (Seat Egress and Walk, Recovery

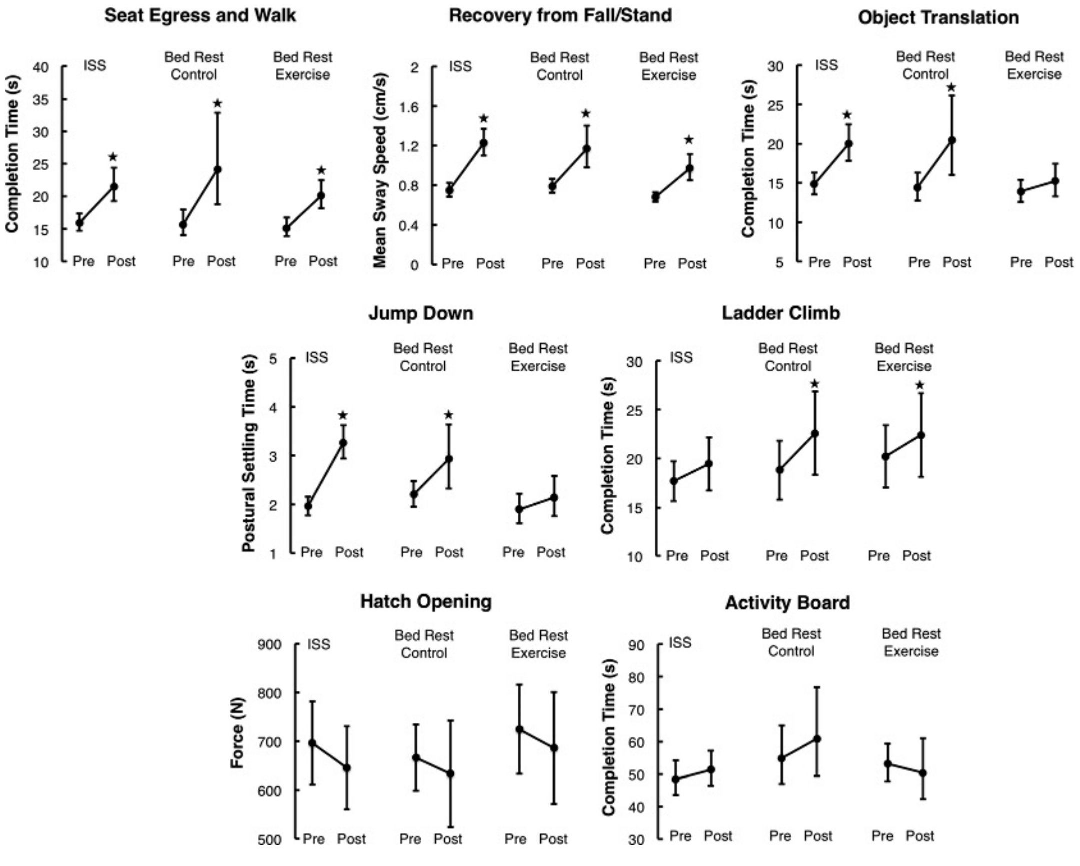

FIGURE 2—Median change in performance of ISS astronauts, and bed rest subjects without (control) and with exercise, on functional tests before (pre) and after (post) spaceflight or bed rest.

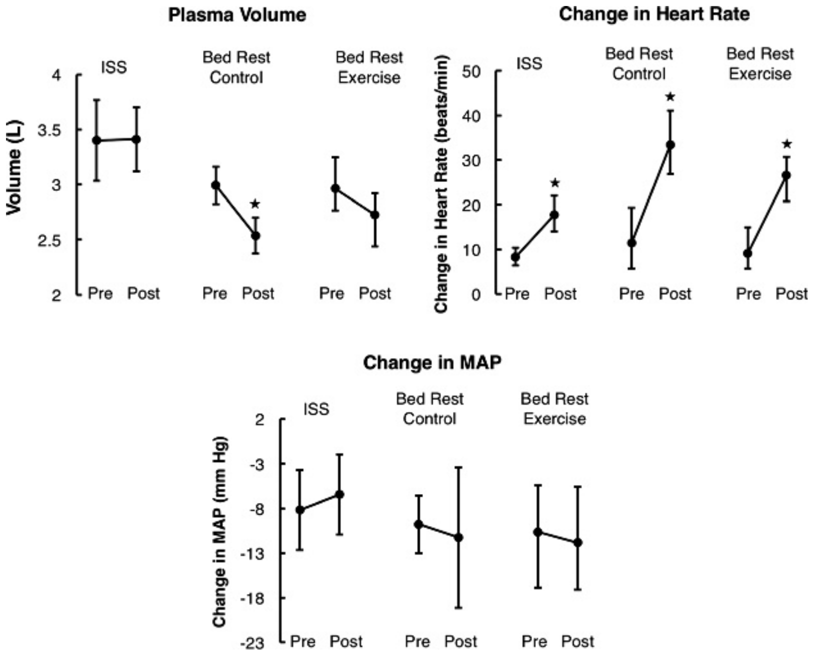

FIGURE 3—Median change in performance of ISS astronauts, and bed rest subjects without (control) and with exercise, on cardiovascular system tests before (pre) and after (post) spaceflight or bed rest.

from Fall/Stand, Object Translation, Jump Down, Ladder Climb) showed the greatest change and significant *P* values (red/pink), whereas functional tests with reduced demand for postural control (Activity Board, Hatch Opening) showed less reduction in performance and were not significantly affected by either spaceflight or bed rest.

For the cardiovascular tests (second section, Table 2, Fig. 3), median plasma volume was not significantly different

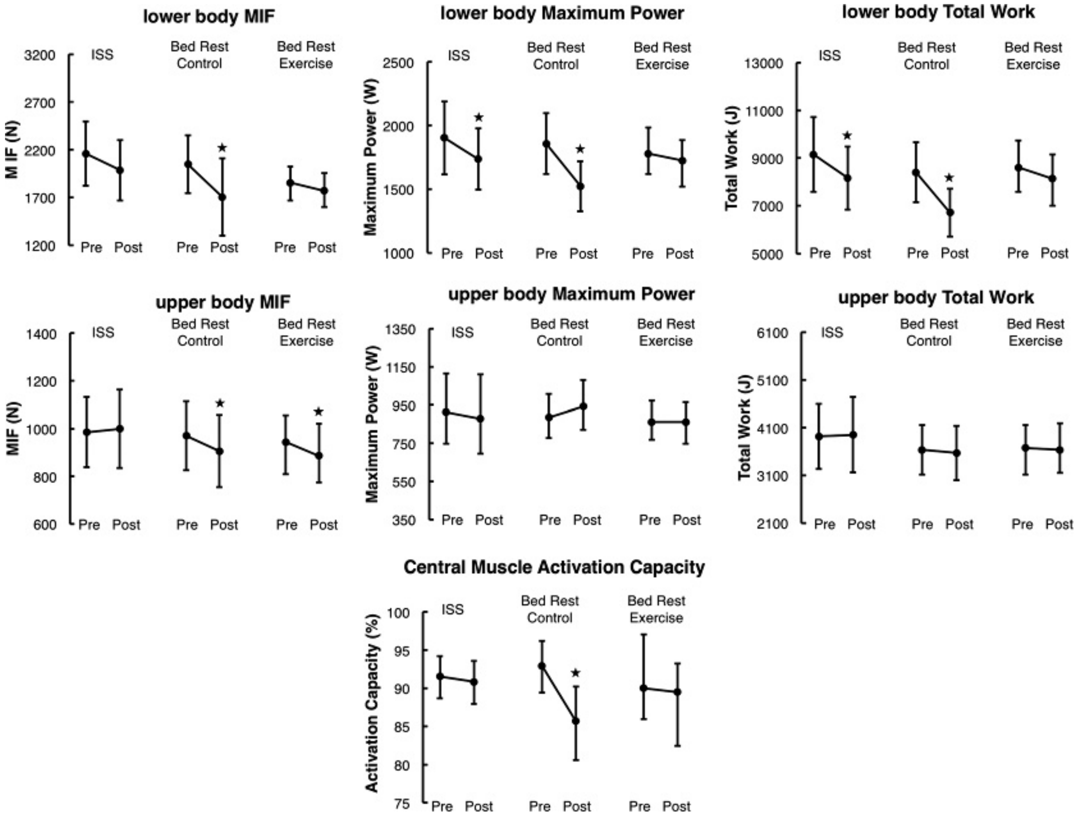

FIGURE 4—Median change in performance of ISS astronauts, and bed rest subjects without (control) and with exercise, on muscle performance tests before (pre) and after (post) spaceflight or bed rest.

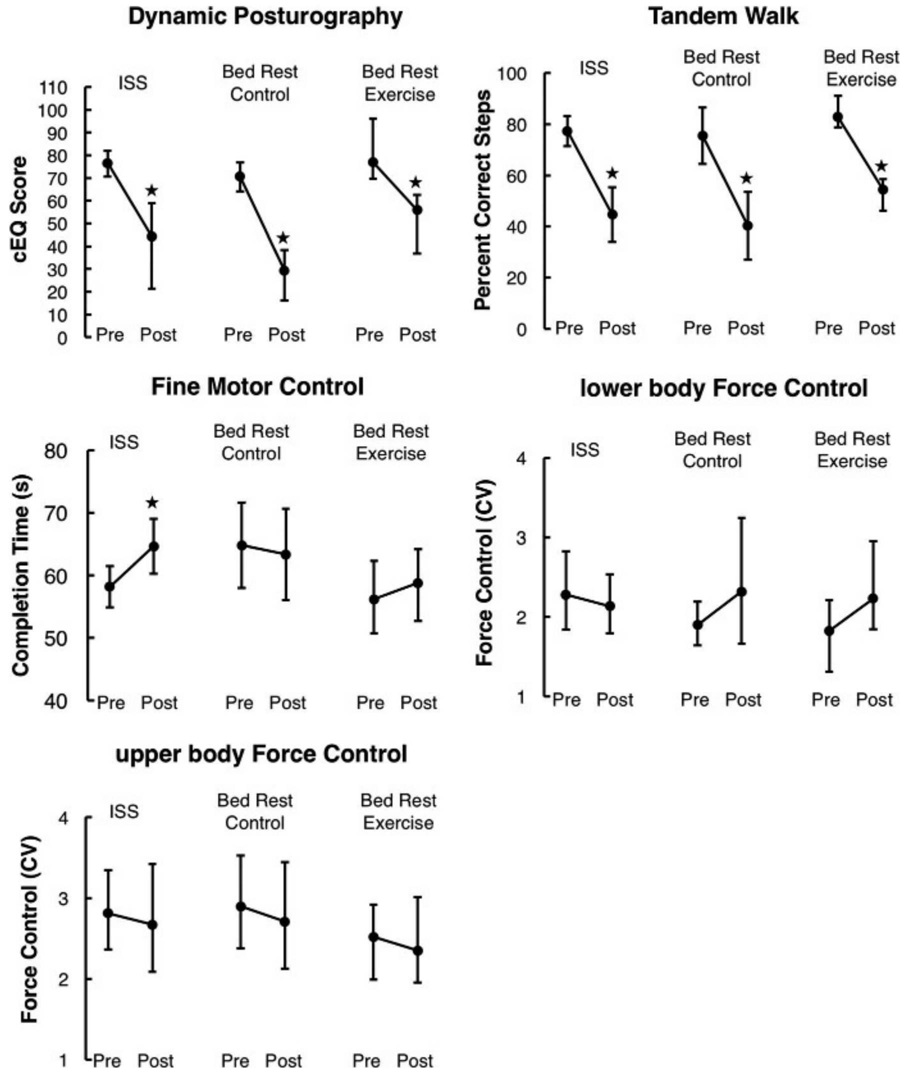

FIGURE 5—Median change in performance of ISS astronauts, and bed rest subjects without (control) and with exercise, on sensorimotor tests before (pre) and after (post) spaceflight or bed rest.

for either ISS or BR-Ex subjects. However, BR-C control subjects experienced a significant drop in plasma volume post bed rest. Results from the Recovery from Fall/Stand Test demonstrated a significant increase in the median Change in Heart Rate from prone to standing orientation for all three subject groups. However, there was no significant difference in the median Change in MAP from prone to standing in any of the groups. In other words, for all subjects, significant increases in median Change in Heart Rate from prone to standing orientation after spaceflight or bed rest occurred with no concurrent noticeable changes in blood pressure.

For the muscle performance test outcomes (third section, Table 2, Fig. 4), ISS subjects experienced a significant reduction in median lower-body Maximum Power and lower-body Total Work. Furthermore, BR-C subjects had a significant reduction in median lower-body MIF, lower-body Maximum Power and lower-body Total Work. In contrast, the BR-Ex subjects did not exhibit a significant reduction in lower-body MIF, lower-body Maximum Power or lower-body Total Work. Both bed rest groups showed a significant reduction in the upper-body MIF measured post bed rest, while in comparison, ISS subjects showed no reduction in upper-body MIF. However, there was no evidence in any of the groups of reduction in upper-body Maximum Power and upper-body Total Work values after spaceflight or bed rest. There was no significant change in central muscle activation capacity in the ISS and BR-Ex subjects, but BR-C subjects showed a significant reduction in this metric. In general, although BR-C and ISS subjects showed significant reduction in lower-body neuromuscular performance, the BR-Ex subjects did not show any major overall change in neuromuscular performance.

For the sensorimotor tests (fourth section, Table 2, Fig. 5), data show a significant reduction in the median cEQ Score for the Dynamic Posturography Test and a significant reduction in the median Percent Correct Steps for the Tandem Walk Test for all three subject groups. Median Completion Time in the Fine Motor Control Test was significantly increased only

TABLE 2. *P* values associated with the effect of spaceflight or bed rest on functional and physiological test outcome measures (variables).

	ISS	Bed Rest Control	Bed Rest Exercise
Functional tests			
Seat Egress and Walk	0.000	0.000	0.000
Recovery from Fall/Stand	0.000	0.000	0.000
Object Translation	0.000	0.000	0.083
Jump Down	0.000	0.003	0.266
Ladder Climb	0.009	0.000	0.007
Activity Board	0.220	0.082	0.366
Hatch Opening	0.046	0.257	0.249
Cardiovascular tests			
Plasma Volume	0.920	0.000	0.045
Change in MAP	0.515	0.588	0.769
Change in Heart Rate	0.000	0.000	0.000
Muscle performance tests			
Lower-body MIF	0.058	0.000	0.119
Lower-body Maximum Power	0.002	0.000	0.271
Lower-body Total Work	0.003	0.000	0.065
Upper-body MIF	0.352	0.002	0.007
Upper-body Maximum Power	0.471	0.033	0.997
Upper-body Total Work	0.659	0.429	0.659
Central Muscle Activation Capacity	0.456	0.000	0.761
Sensorimotor tests			
Dynamic Posturography	0.000	0.000	0.000
Tandem Walk	0.000	0.000	0.000
Fine Motor Control	0.000	0.384	0.148
Lower-body Force Control	0.548	0.153	0.173
Upper-body Force Control	0.537	0.541	0.550

The post-spaceflight and post-bed rest outcome data points were compared with their baseline values. *P*-value threshold for rejection was 0.008, based on the FDR of 0.01. Significant cells are highlighted in red. Marginally significant cells are highlighted in pink ($0.008 < P < 0.009$). Cells in green indicate a *P* value >0.009.

for ISS subjects, suggesting a decrease in fine motor control ability after long-duration spaceflight, but this measure did not change significantly for either bed rest groups. The CV in the Force Control Test did not change for either upper or lower body during the no-visual-feedback condition for all subject groups, indicating no loss in steady state force control ability associated with spaceflight or bed rest. Hence, in general, tests of balance and dynamic gait control (Dynamic Posturography, Tandem Walk) showed the greatest deficits, indicating significantly reduced static and dynamic postural stability after both spaceflight and bed rest.

Mapping the Relationship between Changes in Functional and Physiological Tests

Table 3 shows the values of Somers' *D* (upper number) and the corresponding *P* value in parentheses (lower number) for testing the null hypothesis of no association between changes in physiological and changes in functional test results. Significant associations ($P < 0.003$) between the changes in each functional test and the corresponding change in each physiological variable are highlighted in red. In addition, we have also chosen to highlight the associations with *P* values close to the threshold ($0.003 \le P \le 0.004$) in pink. The 15 physiological outcomes listed are grouped into Cardiovascular, Muscle, and Sensorimotor categories. As with Table 2, the color coding of cells in Table 3 allows the reader to make visual comparisons on a macro level for association between the changes in groups of physiological tests with changes in each functional test. The sign associated with each Somers' *D* value indicates the discordance (negative) or concordance (positive) between the change in the physiological variables and each corresponding change in functional test performance within each subject across the different sessions.

As an example, Table 3 indicates that for the Seat Egress and Walk Test, increases in the Completion Time are significantly negatively associated (in discordance) with decreases in: plasma volume ($D = -0.349$), lower-body MIF ($D = -0.305$), lower-body Maximum Power ($D = -0.319$), lower-body Total Work ($D = -0.293$), Dynamic Posturography ($D = -0.456$), and Tandem Walk ($D = -0.428$); but are significantly positively associated (in concordance) with increases in Change in Heart Rate ($D = +0.398$). It is important to note that in this example, the discordance of the Somers' *D* are in agreement with the median increase in the Completion Time (Fig. 2A) being associated with the decrease in the median estimates of the corresponding physiological performance outcome measures pre to post spaceflight and bed rest (Figs. 3–5). The significant concordance (positive association) found in the example is in agreement with the median increase in the Completion Time for this functional task being associated with the median increase in the Change in Heart Rate measure of cardiovascular performance pre to post spaceflight and bed rest (Fig. 3). We infer the values of the magnitude of Somers' *D* for these physiological variables reflect the relative potential impact that changes in sensorimotor balance control (Dynamic Posturography and Tandem Walk tests), lower limb neuromuscular (lower-body MIF, Maximum Power, and Total Work) and cardiovascular (Change in Heart Rate) outcomes have toward change in performance of the Seat Egress and Walk Test.

Other functional tests which show a similar covariation across the three physiological systems include changes in Completion Time for the Recovery from Fall/Stand and Object Translation tests. Notably, outcomes for both these tests show no significant associations with the change in Plasma Volume. However, the changes in Completion Time for the Object Translation Test show a significant additional concordant association with the changes in the sensorimotor performance of the fine motor control. in contrast, the change in Completion Time for the Ladder Climb Test performance was significantly associated with changes in several cardiovascular (discordant with plasma volume and concordant with Change in Heart Rate) and sensorimotor (discordant with Dynamic Posturography, discordant with Tandem Walk and concordant with Fine Motor Control) variables measuring balance and fine motor control abilities, but only one of the lower-limb neuromuscular variables (discordant with lower-body MIF). Performance on the Activity Board was only in concordance with changes in the sensorimotor outcome of the Fine Motor Control Test. The change in performance for the Jump Down Test was marginally significant in discordance with changes in the

TABLE 3. Somers' *D* association (and *P* value) between changes in each of the 15 physiological test outcome measures (variables) and each of the seven functional test outcome measures across all session pairs within each subject.

	Seat Egress and Walk	Recovery From Fall/Stand	Object Translation	Jump Down	Ladder Climb	Activity Board	Hatch Opening
Cardiovascular tests							
Plasma Volume	−0.349 (0.000)	−0.163 (0.006)	−0.189 (0.005)	−0.133 (0.104)	−0.205 (0.003)	−0.132 (0.058)	0.179 (0.005)
Change in MAP	−0.063 (0.437)	−0.031 (0.669)	0.037 (0.671)	0.061 (0.491)	−0.008 (0.919)	−0.005 (0.940)	−0.081 (0.348)
Change in Heart Rate	0.398 (0.000)	0.472 (0.000)	0.363 (0.000)	0.172 (0.008)	0.246 (0.002)	0.072 (0.304)	−0.170 (0.004)
Muscle performance tests							
Lower-body MIF	−0.305 (0.000)	−0.363 (0.000)	−0.285 (0.000)	−0.149 (0.051)	−0.189 (0.004)	−0.018 (0.766)	0.175 (0.004)
Lower-body Maximum Power	−0.319 (0.000)	−0.361 (0.000)	−0.414 (0.000)	−0.040 (0.611)	−0.181 (0.014)	−0.108 (0.146)	−0.008 (0.906)
Lower-body Total Work	−0.293 (0.000)	−0.462 (0.000)	−0.325 (0.000)	−0.140 (0.056)	−0.218 (0.005)	−0.061 (0.274)	0.106 (0.104)
Upper-body MIF	−0.107 (0.206)	−0.144 (0.079)	−0.112 (0.234)	−0.040 (0.585)	−0.069 (0.325)	0.003 (0.974)	0.032 (0.633)
Upper-body Maximum Power	0.117 (0.030)	−0.003 (0.972)	−0.013 (0.823)	0.008 (0.909)	0.080 (0.197)	0.123 (0.052)	0.079 (0.119)
Upper-body Total Work	0.008 (0.895)	−0.013 (0.863)	−0.003 (0.973)	−0.061 (0.375)	−0.016 (0.837)	0.008 (0.894)	0.053 (0.322)
Central Muscle Activation Capacity	−0.107 (0.191)	−0.162 (0.054)	−0.217 (0.006)	−0.174 (0.028)	−0.101 (0.203)	0.009 (0.878)	0.058 (0.443)
Sensorimotor tests							
Dynamic Posturography	−0.456 (0.000)	−0.319 (0.000)	−0.388 (0.000)	−0.230 (0.004)	−0.232 (0.000)	−0.069 (0.364)	0.119 (0.043)
Tandem Walk	−0.428 (0.000)	−0.507 (0.000)	−0.368 (0.000)	−0.201 (0.005)	−0.291 (0.000)	−0.179 (0.009)	0.090 (0.123)
Fine Motor Control	0.210 (0.010)	0.057 (0.415)	0.235 (0.001)	0.107 (0.129)	0.226 (0.000)	0.279 (0.000)	0.048 (0.478)
Lower-body Force Control	0.048 (0.474)	0.000 (1.000)	−0.022 (0.780)	−0.022 (0.691)	0.100 (0.080)	0.022 (0.650)	−0.017 (0.785)
Upper-body Force Control	−0.084 (0.239)	−0.089 (0.115)	−0.141 (0.034)	−0.011 (0.869)	−0.008 (0.894)	0.026 (0.731)	0.003 (0.972)

When *D* is positive, the primary direction of change is the same for both types of variable (both increase or both decrease). When *D* is negative, the primary direction for change in the physiological variable is opposite the primary direction of change in the functional test variable (one increases and the other decreases). Cells with significant values of *D* are highlighted in red, indicating a *P* value < 0.003, based on controlling the FDR to 1%. Marginally significant cells ($0.003 < P < 0.004$) are highlighted in pink. Cells in green indicate a *P* value >0.004.

sensorimotor variable cEQ Score measuring balance control ($P = 0.004$). The change in performance in the Hatch Opening Test shows marginally significant association in discordance with the changes in the cardiovascular variable measuring Change in Heart Rate ($P = 0.004$) and in concordance with changes in the neuromuscular variable measuring lower-body MIF ($P = 0.004$).

DISCUSSION

In general, the results of this study indicated that ISS subjects 1 d after their return from 6 months of spaceflight showed a significant median decrease in performance for the functional tasks that have a greater requirement for body coordination and postural stability control: Seat Egress and Walk, Recovery from Fall/Stand, Object Translation, Jump Down, and Ladder Climb. Functional tests with reduced requirements for postural stability (i.e., Hatch Opening, and Activity Board Test) showed little reduction in performance. These functional changes were paralleled by similar decrements in sensorimotor tests that assessed postural and dynamic gait control. Other changes included reduced lower limb muscle performance and increased HR that served as a compensatory response to maintain blood pressure. Exercise performed during bed rest prevented detrimental change in neuromuscular and cardiovascular function, however, both BR-C and BR-Ex groups experienced functional and balance deficits similar to spaceflight subjects.

In general, changes in all three physiological systems measured in this study (i.e., the sensorimotor, cardiovascular and neuromuscular system) were found to have appropriate covariations to changes in functional performance in accordance with the requirements for each functional task. Further, these associations suggest the importance of maintaining and improving upon current inflight exercise regimens to mitigate the cardiovascular and neuromuscular physiological systems. In addition, there is a specific need for a countermeasure to mitigate postflight postural control dysfunction that is independently impacting functional performance after long-duration spaceflight.

Effects of Spaceflight and Bed Rest on Functional and Physiological Tests

Functional tasks. In this study, tasks that required body coordination, postural stability and functional mobility showed significant decrement in performance after both spaceflight and bed rest. Previously, locomotor control and segmental coordination were shown to be degraded after both short- and long-duration spaceflights (34–44). In our previous study, astronauts after long-duration spaceflight also showed impaired functional mobility increasing their median time to complete an obstacle course by 48% compared with their preflight times (2). In our current study, although the 31% increase in median time to complete the Seat Egress and Walk Test was significant for ISS subjects after spaceflight, the magnitude of change was less than that observed in our previous study. The main difference between the two studies was that subjects in our present study were not challenged by walking on a compliant foam surface, as was the case in the previous study. In general, walking on such a foam surface increases the instability of the upper body as compared with a solid surface (45) and increases the reliance on vestibular derived information (46). Corresponding increased median Completion Times seen in the BR-C group (38%) and in the BR-Ex group (23%) in this study were consistent with the 27% increase in Completion Time of an obstacle course after 60 d of HDT bed rest in our previous bed rest study (11).

In the current study, we observed that for the Object Translation Test, ISS subjects showed greater increase in median Completion Time (58%) than BR-C subjects (26%) or BR-Ex subjects (no noticeable change). Thus, based on the BR-Ex subjects' performances on the Object Translation Test, the SPRINT exercise protocol during bed rest appeared to be beneficial and sufficient in maintaining performance in this functional task. However, this SPRINT exercise protocol during bed rest was not sufficient to maintain performance on mobility tasks such as the Seat Egress and Walk Test that required a higher demand on postural control and coordination.

The Recovery from Fall/Stand Test showed a median increase in the velocity of postural sway in the ISS (66%), BR-C (54%) and BR-Ex (42%) subject groups. These data indicate that after both spaceflight and bed rest, subjects show reduced postural equilibrium control after a change in postural orientation that also induced an orthostatic challenge. The cardiovascular system was challenged as the median Change in Heart Rate from prone to standing was significantly greater after spaceflight or bed rest in all subject groups. Importantly, the reduction in postural stability control could not be ascribed to reduced blood pressure, as the median MAP was not noticeably changed during this test in all subject groups.

In our study, performance on the Jump Down Test (Postural Settling Time) was significantly worse in the ISS subject group, showing a 58% median increase with respect to preflight values. The degraded Jump Down Test performance seen postflight may reflect altered central interpretation of otolith acceleration cues and changes in vestibulospinal and somatosensory spinal reflexes. In a previous study, we investigated the effects of spaceflight on two-footed jump landings in shuttle astronauts using the same Jump Down Test paradigm (47). Similar to the present results, Newman et al. (47) found that there was significant postural instability after floor impact after the jump. They attributed this decrement to postflight changes in motor programming during the jump aerial phase, impaired ability to prepare the limb muscles, and compensatory activations for dealing with the impact phase of the jump (47). Other studies have shown that after spaceflight, astronauts experienced changes in otolith-spinal reflex function and abnormal levels of muscle spindle receptor activation, which resulted in misinterpretation of muscle length and the subsequent abnormal flexion that is essential for the preprogrammed motor strategies used for impact absorption and postural stability after a jump (48–51). By comparison, after bed rest, BR-C subjects showed only a 26% median increase in Postural Settling Time, while no noticeable change was seen in the BR-Ex subjects. Dupui et al. (52) have argued that long-term exposure to bed rest does not affect the signaling from the semicircular canals or the otoliths. In bed rest, despite the fact that gravity is present, the body primarily undergoes axial unloading and this reduces inputs to the somatosensory receptors of the feet along with those distributed throughout the body. We infer that the increased decrement in the Jump Down Test response shown in spaceflight subjects reflects the combined changes in both vestibulospinal and somatosensory systems, whereas the reduced decrement in the Jump Down Test response shown in bed rest subjects reflects alterations predominately in somatosensory function.

Performance on the Activity Board and Hatch Opening tests was not noticeably changed by either spaceflight or bed rest, presumably because posture was stabilized while the task was being performed. For example, in the Hatch Opening Test posture was stabilized because subjects completed the task while gripping the hatch-like wheel device. In the Activity Board Test, postural instability was potentially minimized because subjects performed the task while intermittently using the board as a stable reference point. Postural stability can be adequately stabilized using a light finger touch on a stationary surface even when the level of force is inadequate to physically stabilize postural sway (53,54). This capability could have played a role in reducing postural instability in these tests.

Cardiovascular system. Exposure to spaceflight and bed rest have been previously associated with a decrease in plasma volume that has been suggested to contribute to increased HR and decreased arterial blood pressure while standing after spaceflight and bed rest. Plasma volume loss is an early consequence of exposure to bed rest and spaceflight that does not appear to worsen progressively as the duration of exposure lengthens (10,55,56). Previous authors have reported that despite astronauts participating in an end-of-mission fluid loading protocol in the hours before landing, their plasma volume was decreased 7% to 20% soon after landing for shuttle flights; similar plasma volume loss has been reported after long-duration missions aboard the Mir Space Station (55–60). Contrary to this, in our current study, plasma volume was unchanged pre to post spaceflight in the ISS astronauts. The disparity between these current results and previous observations likely occurred because these astronauts were not studied until 1 d after returning to Earth and often receive intravenous saline in the hours immediately after landing. Plasma volume has been shown to recover after landing, with an overshoot by 3 d postlanding

(59). Further, in our current study BR-C subjects experienced a significant drop in plasma volume (13%) post bed rest. However, like the ISS subjects, the BR-Ex subjects also experienced no change in plasma volume, even though these subjects did not complete the fluid loading countermeasure used by astronauts and plasma volume was measured before rising on the first day of testing after bed rest. It is possible that the intense nature of bed rest exercise countermeasures contributed to the maintenance of plasma volume in these subjects (61,62).

As an assessment of orthostatic intolerance, this current study is the first to implement an operationally-oriented stand test on ISS crewmembers returning from long-duration spaceflight. This study measured cardiovascular responses to 3.5 min of standing after rising from a prone position. Previously, we have reported that >60% of astronauts participating in long-duration spaceflight could not complete a 10 min 80° head-up tilt test on landing day (3,56). Similarly, previous investigators have reported a high incidence of orthostatic intolerance after HDT bed rest (10,63). No subject experienced presyncope during this relatively brief stand test but, based upon results from our previous study in ISS astronauts (3), the test duration was chosen to minimize the risk of these subjects developing signs of presyncope that might have precluded their participation in subsequent tests on the same day. A progressive decrease in arterial blood pressure often precedes presyncope, but that was not apparent in these subjects. The median Change in MAP from prone to standing did not change from pre to post spaceflight or bed rest in ISS, BR-C, and BR-Ex subjects during 3.5 min of standing.

Orthostatic intolerance is manifested to varying degrees in almost all astronauts after spaceflight, with symptoms ranging from an increased HR to presyncope while upright. In this study, a significantly greater median Change in Heart Rate in response to standing was measured in ISS subjects (102%), BR-C subjects (130%), and the BR-Ex subjects (158%), likely as the mechanism to maintain MAP during the Recovery from Fall/Stand Test. Of the three groups studied, however, only the BR-C subjects experienced a concomitant decrease in plasma volume, which may have contributed to the appearance of a greater HR response during the post bed rest stand test. Clearly though, plasma volume loss is not the only mediator of an exaggerated response to standing. For example, we have previously reported that plasma volume losses were not different between subjects who become presyncopal and those who did not during a tilt test after spaceflight. This finding is also supported by the observation of maintained plasma volume in ISS and BR-Ex subjects in this study. Cardiac atrophy has been suggested to play a role in post–bed rest orthostatic intolerance (12), but cardiac mass and some measures of unstressed cardiac function were maintained in the BR-Ex subjects. No similar cardiac atrophy measures were available for the ISS astronauts in this study, but their inflight exercise countermeasures were similar in goal to those performed by the BR-Ex subjects in that both were designed to mitigate impairment of aerobic capacity/cardiovascular function. Several studies have provided evidence that autonomic function is impaired after spaceflight, and some have indicated the potential role of vestibular maladaptive changes in orthostatic intolerance experienced by returning astronauts (64–66). It is important to note that neither the current exercise countermeasures as part of the SPRINT protocol nor the current inflight exercise regimens may have helped to protect against these dysfunctions. Hallgren et al. (64) recently demonstrated a significant relationship between otolith dysfunction and change in MAP using a tilt table test after a long-duration (6 months) exposure to microgravity. Operationally other factors, such as voluntary contractions of the lower limb muscles that are capable of generating required venous return to the heart to partially offset the gravitational pull (67) and increased sympathetic activity in preparation to movement (68), may also play an additive role.

Neuromuscular function. After spaceflight, during which astronauts participated in exercise countermeasures, degradation in muscle performance was generally noticeably greater in the lower body than in the upper body as shown by the significant reductions in the lower-body Maximum Power (8%) and lower-body Total Work (10%). However, none of the other diverse neuromuscular assessments showed a significant degradation after spaceflight. By comparison, BR-C subjects (no exercise) demonstrated a significant reduction in lower-body MIF (18%), lower-body Maximum Power (14%) and lower-body Total Work (19%) as well as degradation in the upper-body MIF (9%) and the central muscle activation capacity (10%). Importantly, the BR-Ex group participating in the SPRINT exercise prescription showed no significant change in any of the diverse neuromuscular assessments spanning the upper and lower bodies except for a small but significant decrease in the upper-body MIF (5%).

Muscle strength has been assessed using various methods in both spaceflight and bed rest analog studies and has shown significant losses in the ankle, knee, hip and trunk joints and the muscles spanning them (5). A number of studies have attributed the excessively large loss of muscle strength after prolonged periods of disuse to alterations in neural drive (69–72). Our results from the current study showing the median changes on the lower-body strength measures of MIF, Maximum Power, and Total Work are similar to or comparatively less than what has been previously reported. However, in this study, the neural drive as assessed in the quadriceps showed a significant drop of around 10% after bed rest in only the BR-C subjects and showed no change in the ISS and BR-Ex group of subjects. Thus, in this study, bed rest subjects who performed SPRINT, an integrated high-intensity interval-type resistance and aerobic training program, while in bed rest, maintained lower-body muscle performance after bed rest. It is important to note that the BR-Ex subjects and ISS crewmembers performed different exercise programs. More importantly, exercise regimens for bed rest subjects and astronauts share a common goal of being designed to mitigate loss of aerobic function and muscle mass and strength. Exercise was performed 6 $d \cdot wk^{-1}$ in both groups. Bed rest subjects did not do upper-body training but performed lower-body resistance exercise 3 $d \cdot wk^{-1}$, whereas astronauts performed upper- and lower-body resistance exercise up to 6 $d \cdot wk^{-1}$. Aerobic exercise training was performed 6 $d \cdot wk^{-1}$ for both bed rest subjects and astronauts. Bed rest subjects' aerobic exercise consisted of 3 $d \cdot wk^{-1}$ continuous exercise on a supine cycle ergometer and 3 $d \cdot wk^{-1}$ of interval training on a horizontal treadmill. Astronaut aerobic training also included continuous and interval training on a cycle ergometer and treadmill a total of 6 $d \cdot wk^{-1}$; however, the type of session and choice of hardware was crewmember-specific and therefore varied from person to person.

Sensorimotor system. The results of this study indicated that for ISS subjects after spaceflight, the median cEQ Score was significantly decreased by 59%, the median Percent Correct Steps was significantly decreased by 40%, whereas the median Completion Time for the Fine Motor Control task was significantly increased by 10%. However, results from the upper- and lower-body Force Control Test did not noticeably change. Similarly, for BR-C subjects after bed rest, the median cEQ Score and median Percent Correct Steps showed significant decreases of 63% and 51%, respectively, while for BR-Ex subjects, corresponding decreases were still significant but smaller, being 17% and 33%, respectively. Bed rest did not noticeably affect the performance of the Fine Motor Control Test or the tests of upper- and lower-body force control in either group of bed rest subjects. Overall, both spaceflight and bed rest subjects showed significant reduction in static and dynamic balance control abilities with the additional finding that after spaceflight there was also a reduction in fine motor control abilities.

The Dynamic Posturography Test was conducted with the eyes closed, while making pitch head movements and standing on a sway-referenced support surface intended to disrupt somatosensory feedback. This test condition is nominally designed to measure how well vestibular input can be utilized to maintain balance during quiet stance. Significant decrements were observed in the performance of this test in both spaceflight and bed rest subjects. Although the decrease in the median cEQ Scores postflight in ISS subjects was significantly reduced, it was comparatively smaller 1 d after spaceflight to that reported in previous studies (1,23). Static and dynamic balance control has been shown to be significantly affected after bed rest, despite the fact that subjects performed various resistive and cardiovascular exercises (11,52,73). In our current study, exercise during bed rest in the BR-Ex group resulted in a reduced postural control deficit compared to that shown in the ISS and BR-C groups of subjects. However, this decrement was significant and persisted in the BR-Ex subjects, indicating that resistance and cardiovascular exercise were not sufficient to mitigate postural instability. ISS subjects in previous evaluations of postural stability had used the interim resistive exercise device (iRED) for resistance exercise. The ARED provides twice the loading capacity of the iRED. In addition to attenuating loss of bone mineral density and muscle mass (74), exercise on the ARED was associated with less decrement in crewmembers' postflight postural stability and agility scores compared to those who had used iRED (23). The increased body loading during ARED exercises may have provided greater postural control challenges during exercise, thus providing some improvement in postflight balance performance. Despite these improvements in postural stability scores with ARED exercise, subjects still exhibited decrements in postflight postural control.

The purpose of the Tandem Walk Test was to assess changes in dynamic balance control. This test has been used as an indicator of vestibular driven ataxia and was shown to have high validity (25). Further, deficits in postural control ability during tandem stance on rails has also been shown to be reduced to 40% to 90% after short-duration flights (75). Dynamic balance has been tested using a Tandem Walk Test on rails in 60 d HDT bed rest studies and found that bed rest significantly reduced the time and distance that subjects who did not exercise could walk on rails in tandem heel-to-toe walking post bed rest (76). In our study, the Tandem Walk Test showed a similar decrement in performance after spaceflight and bed rest (with and without exercise).

It has been generally maintained that inflight reinterpretation of vestibular inputs during the adaptation process to the microgravity environment serves as the primary cause for postflight dysfunction in control of postural stability (1,77). However, in our study, BR-C and BR-Ex subjects also showed a significant degradation in postural control abilities in both the Dynamic Posturography and Tandem Walk tests. Dupui and coworkers (52) have argued that exposure to prolonged bed rest should not affect signaling from the semicircular canals or the otoliths. In bed rest, the body undergoes axial unloading, despite the fact that gravity is present, and this reduces inputs to the somatosensory receptors distributed throughout the body. Proprioception and body-load sensors play an integral role in the control of gait and postural equilibrium (c.f. 11). It has been hypothesized that the body unloading and subsequent loss of support afferentation experienced during spaceflight induces a cascade of neuromotor alterations leading to neuromuscular dysfunction including loss of tonic muscle activation and subsequent postflight postural and locomotor instability (78,79). Watt and colleagues (51) asked astronauts to perform deep rhythmic knee and arm bends with the appropriate restraints during and after spaceflight. Subjects reported postflight illusions of floors and walls moving toward them depending on the plane of subject motion, and that their knees bent more rapidly than intended. This can be partly explained by an abnormal level of muscle spindle receptor activation on return to 1*g*, which results in misinterpretation of muscle length and subsequent abnormal flexion. A more recent study investigated the impact of spaceflight-induced changes in the level of foot skin sensitivity on postflight postural disequilibrium (80). Skin sensitivity of shuttle astronauts was measured as vibration perception at the great toe, fifth metatarsal and heel. Both increase in sensitivity to the fast-adapting (FA) skin receptors in a subset of subjects and an overall decrease in sensitivity for the slow-adapting (SA) receptors were observed postflight. No relationship was found between the reduction in sensitivity of the SA receptors and change in balance control (80). Subjects showing hypersensitivity in the FA receptors showed greater reduction in postural equilibrium control compared to non-hypersensitive FA receptor participants using the same Dynamic Posturography protocol as in this study, pointing to the importance of foot skin receptors in maintaining balance control and its role in postflight postural disequilibrium (80). These results point to the importance of proprioceptive and skin receptors in maintaining balance control and suggest that changes in the central interpretation of information from the muscle spindles and skin receptors also contribute to postflight postural disequilibrium.

Recent neurophysiological studies support the notion that when vestibular information becomes unreliable, supplemental information such as proprioception is up-weighted to maintain control of posture and locomotion (81,82). More importantly, the activity of vestibular nucleus neurons serves to integrate information from multiple sensory sources, such as the labyrinth, the neck, and the spinal cord, including proprioceptive signals from the limbs (43,83). Therefore, together with the results from our bed rest study and previous spaceflight studies, we infer that measures obtained from the Dynamic Posturography and Tandem Walk tests are reflective of changes seen as a result of adaptation to somatosensory inputs after bed rest, or a combination of alterations in both somatosensory and vestibular information after spaceflight.

In the current study, fine motor control was altered in spaceflight subjects, but there was no change in the two groups of bed rest subjects. The test for fine motor control used in this study involved a keyed pegboard test in which subjects sitting in a chair were required to reach and grasp a peg, pick it up, and place it with appropriate orientation to match the keyed slots on the board. Previous studies have shown that basic tasks, such as pointing, reaching, and grasping, were impaired during spaceflight missions as well as those done on parabolic flights and during centrifugation (84–88). Others have found that forces applied to the laparoscopic tool handles during knot tying were increased while knot quality was decreased during the weightless phases of parabolic flight compared with ground control sessions (89).

For all subject groups, performance on the Force Control Test did not change noticeably postflight or post–bed rest for both upper- and lower-body force control performance without visual feedback, indicating no loss in steady state force control ability associated with spaceflight or bed rest similar to past spaceflight studies. Further, results from previous spaceflight studies show that the temporal parameters of movements made and the number of discernable handle positions to reproduce several descrete levels of force did not change (90) nor did the ability to maintain a static level of force during a force matching task without vision (91). These results are similar to our findings even though the targeted force output in our tests was set at the reduced levels of 5% of MIF, as this was considered to be sensitive to changes in elderly subjects (92) as well as in other bed rest studies (93).

Mapping the relationship between changes in functional and physiological tests. As shown in Table 3, fall in Plasma Volume was associated with reduced performance in the Seat Egress and Walk and Ladder Climb tests, suggesting that plasma volume losses affect tasks requiring prolonged whole body upright exercise. Decreased plasma volume alone can result in a reduction in aerobic capacity and an elevated HR at rest and during exercise. Given that these are common observations after bed rest and spaceflight, it is not surprising that we observed associations between Plasma Volume and changes in functional task tests. In some cases, this association can be explained by concurrent changes in different physiological systems, but in tasks that require significant physical work there may be a more direct relationship. Decreased aerobic capacity, changes in oxygen uptake kinetics, and increased perception of effort could thus contribute to slower performance times. Further, there was no evidence that changes in performance of functional tasks requiring upright posture, but without a significant physical work requirement (Recovery from Fall/Stand, Activity Board, and Hatch Opening) were associated with changes in plasma volume. Changes in Heart Rate were positively associated with changes in functional tasks that stressed the cardiovascular system due to upright posture for an extended period of time (Seat Egress and Walk, Recovery from Fall/Stand, Object Translation, Ladder Climb, and Hatch Opening). Importantly, there is no evidence that changes in any of the functional tasks demonstrated a significant association with a change in arterial blood pressure. This suggests either that decrements in performance for these functional tasks, which represent generic functional elements of mission tasks, do not result from a fall in arterial pressure or that the arterial pressure was adequately maintained through other compensatory mechanisms, such as an elevated HR. However, the increases seen in the Change in Heart Rate cardiovascular variable from prone to standing is significantly associated with decreases in a number of functional task outcomes, highlighting that if tasks require greater activation of the cardiovascular system, it is possible that the increased HR would not sufficiently maintain arterial pressure.

Reduced performance in functional tasks requiring full body movement, segmental coordination, and postural control (Seat Egress and Walk, Recovery from Fall/Stand, Object Translation) were significantly associated with decrements in lower-body neuromuscular performance metrics. Changes in the Jump Down and Activity Board tasks showed no association with the reductions in lower-body neuromuscular performance metrics, indicating that lower-body neuromuscular changes did not appear to impact these activities significantly. The upper-body neuromuscular performance may be sufficiently maintained, and hence, there was no evidence of association between the change in performance of any of the functional tasks and the changes in upper-body neuromuscular function.

Changes in metrics of balance control during static and dynamic movement conditions (Dynamic Posturography, Tandem Walk) tended to be associated with changes in performance of functional tasks with greater demand for balance control (Seat Egress and Walk, Recovery from Fall/Stand, Object Translation, Ladder Climb, Jump Down). This result further supports the observation that, after both spaceflight and bed rest, declines in postural control likely result in declines in performance of functional tasks with high postural equilibrium demands. Interestingly, for the Activity Board Test, there was a significant association with decrement in the Fine Motor Control Test. This is further corroborated by the significant association seen in changes in Fine Motor Control with performance on the Object Translation Test, which also requires adequate reaching, grasping and object manipulation ability to successfully perform the task. Additionally, changes in the Ladder Climb Test were significantly associated with alterations in Fine Motor Control. The foot is the end-effector of a kinematic chain (leg) and positioning of the feet is important for tasks such as the Ladder Climb, especially in cases where visual feedback is unavailable during the performance of the task. Previous studies have established increased variability in the kinematics of the hip and knee joints during postflight treadmill walking and significant changes in foot clearance after spaceflight (39,41). Data have been published on pointing tasks in which the arm is the kinematic chain with the pointing finger as the end-effector. These data show that variability of finger position is significantly elevated 1 d after spaceflight in cyclical hand-tracking trajectories (94). Hence, the association between performance changes seen in the Ladder Climb Test and alterations in Fine Motor Control Test could be ascribed to possible increased variability of the foot as an end-effector. This may lead to misaligned foot placement during ladder climbing, resulting in increased time to complete the task.

Implications for countermeasures. Our study results confirm the integral role of resistance and aerobic exercises in maintaining muscle and cardiovascular function during missions, which help in reducing decrements in functional performance. It appears that the SPRINT exercise program was effective for preserving muscle function despite 70 d of exposure to bed rest. It helped maintain performance on the Object Translation and Jump Down tasks which challenged the postural control system, but was not sufficiently effective on functional tasks having more complex requirements of body coordination and postural control, such as Seat Egress and Walk, Recovery from Fall/Stand and Ladder Climb. Countermeasures to reduce headward fluid shift may be an over arching goal; however, it is important to restore cardiovascular performance after spaceflight through the continued efforts to restore plasma volume using fluid and salt loading and intravenous saline administration along with inflight exercise programs and compression garments. In addition, our results also point to the importance of supplementing the inflight exercises that can help improve coordination, balance and mobility functions to help maintain functional performance postflight. The proprioceptive system is a viable countermeasure target given current spaceflight constraints (11,37,78,95–98). Further, results from recent neurophysiological studies indicate that when vestibular information becomes unreliable, supplemental information like proprioception is up-weighted to maintain control of posture and locomotion (81,82). Its role in balance and postural control may be large enough that a well-optimized inflight proprioceptive countermeasure designed to maintain balance function coupled with preflight sensorimotor adaptability training (99) could protect crewmembers enough to perform critical mission tasks. This is a particularly important finding, because historically, it has been believed that vestibular changes were predominantly responsible for the deficits in balance and postural control.

LIMITATIONS

(A) All astronauts perform some inflight exercise countermeasures, their data alone would not allow us to discern the effects of exercise vs. no-exercise. (B) Further, astronaut data collection immediately upon landing for this study was not possible given the remote landing site and complexity of the experimental paradigm. (C) HDT bed rest is an imperfect model of spaceflight and that all aspects of the head ward fluid shifts that occur in spaceflight and HDT bed rest are not completely matched (100,101). (D) Every attempt was made to recruit, from the general public, appropriate age groups matched to the astronaut group at NASA for the bed rest arm of this study (16). However, because of multiple constraints, the demographics of the bed rest group matched in general but was not exactly concordant with the astronaut group.

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