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Exercise Training Mitigates Multisystem Deconditioning during Bed Rest

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Abstract

Introduction—This study investigated the safety and effectiveness of a new integrated aerobic and resistance exercise training prescription (SPRINT) using two different sets of exercise equipment: a suite of large International Space Station-like exercise equipment similar to what is found on the International Space Station and a single device with aerobic and resistance exercise capability in the spaceflight analog of bed rest (BR).

Methods—Subjects ($n = 34$) completed 70 d of 6° head down tilt BR: 9 were randomized to remain sedentary (CONT), 9 to exercise training using traditional equipment (EX), 8 to exercise using traditional equipment and low-dose testosterone supplementation (ExT), and 8 to exercise using a combined resistance and aerobic flywheel device. Peak aerobic capacity, ventilatory threshold, cardiac morphology and function (echocardiography), muscle mass (magnetic resonance imaging) and strength/power (isokinetic, leg press, and vertical jump), and bone health (bone mineral density, blood and urine bone markers) were assessed before and after BR.

Results—The SPRINT protocol mitigated BR-induced muscle and cardiac deconditioning regardless of the exercise device used. Molecular markers of bone did not change in the CONT or EX groups. Peak aerobic capacity was maintained from pre-to post-BR in all exercise groups similarly, whereas significant declines were observed in the CONT group (~10%). Significant interaction effects between the CONT group and all EX groups were observed for muscle

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performance including leg press total work, isokinetic upper and lower leg strength, vertical jump power, and maximal jump height as well as muscle size.

Conclusions—This is the first trial to evaluate multisystem deconditioning and the role of an integrated exercise countermeasure. These findings have important implications for the design and implementation of exercise-based countermeasures on future long-duration spaceflight missions.

Keywords

SPACEFLIGHT; COUNTERMEASURES; FITNESS; INTEGRATIVE PHYSIOLOGY; PERFORMANCE

Dramatic declines in fitness occur with unloading induced by spaceflight, bed rest, and other forms of immobilization. Unmitigated loss of muscle cross-sectional area (CSA) is approximately 0.4% per day for the thigh and calf muscles (1), whereas aerobic capacity declines at a rate of about 0.35% per day (2). Exercise is the only known mitigation against such declines and is routinely used during spaceflight to protect crew health and performance, although the details concerning how exercise can be optimized are lacking. Hospital-based deconditioning and immobilization from casting and/or unloading are rarely treated with formal exercise programs, in part because patients may not tolerate exercise and in part because of lack of proven efficacy or optimization of exercise programming in this population.

Bed rest, particularly in the head down tilt configuration, is used as an analog of spaceflight and offers advantages with respect to the ability to manipulate conditions and research design, better control of confounding factors and risk, and afford considerably faster throughput of subjects. Exercise is the only operational countermeasure against loss of cardiovascular and musculoskeletal health, and all crew members aboard the International Space Station (ISS) participate in daily exercise. Typically, exercise bed rest studies have focused evaluation on either aerobic exercise with cardiovascular outcomes or resistance exercise with musculoskeletal outcomes in attempt to better understand each form of exercise separately. Because crew members perform concurrent aerobic and resistance exercise, it is necessary to optimize an integrated exercise program using exercise timing, schedules, and equipment similar to that aboard the ISS including a cycle ergometer, treadmill, and resistance exercise.

One of the challenges for space travel beyond the ISS is the development of effective exercise countermeasures for future exploration vehicles that are highly restricted in allocations for exercise hardware volume, mass, and power. Currently, small exercise devices that combine aerobic and resistance exercise in a single device are being developed for use on future exploration spaceflight vehicles. Because of potential performance limitations of exploration exercise devices, it is possible that pharmacological interventions may be needed to optimize the effects of exercise countermeasures. Testosterone, given its role in bone and muscle maintenance, is often considered as a potential adjunct countermeasure for unloading-induced atrophy (3). As such, testosterone might enhance the effectiveness of exercise during unloading. However, it is unknown whether an optimized exercise prescription incorporating higher-intensity aerobic and resistance exercise,

testosterone supplementation, and/or novel exercise hardware could mitigate multisystem deconditioning. Accordingly, the primary purpose of this study was to evaluate the effectiveness of a new integrated aerobic and resistance exercise training prescription using two different sets of exercise equipment: a suite of ISS-like exercise equipment and a single device with aerobic and resistance exercise capability.

METHODS

Overview of Research Design

This was a randomized controlled experiment; group assignment was nonblinded with the exception of testosterone, which was administered in a double-blind manner. The study was approved by both the NASA Johnson Space Center and University of Texas Medical Branch institutional review boards, and all subjects provided written informed consent.

The study protocol and screening process is described in detail in the companion paper (4). In brief, potential subjects were prescreened using an online application or via telephone interviews conducted by the NASA Johnson Space Center Test Subject Facility nursing staff. Candidates who met the basic inclusion criteria were asked to complete a second application, which included a log of their daily physical activity, consent for a background check, health history questionnaire, and a NASA-modified Air Force Class III physical examination. Qualified study candidates performed an upright peak cycle ergometry test and an isokinetic knee extension test at $60^{\circ}\cdot\text{s}^{-1}$. Minimum levels of cardiorespiratory fitness (peak aerobic capacity ($\dot{V}\text{O}_{2\text{peak}}$) $>30\text{ mL}\cdot\text{kg}^{-1}\text{ min}^{-1}$) and lower body muscle strength relative to body mass (knee extension $>2.0\text{ N}\cdot\text{m}\cdot\text{kg}^{-1}$) were required to enter the study; these fitness levels represent the lower end of the range in the astronaut corps.

After initial testing, participants were randomized to 1 of 4 intervention groups. Three exercise groups were asked to perform the same high-intensity exercise prescription $6\text{ d}\cdot\text{wk}^{-1}$ during 70 d of bed rest, beginning on the first day in bed. One group used traditional exercise equipment similar to that found on the ISS with no supplementation (EX), the second group used the traditional exercise equipment and was given a testosterone supplementation (ExT), and the third group used a single compact flywheel rowing and resistance exercise device (FLY). The fourth group consisted of control subjects (CONT) who participated in all pre-, in-, and post-bed rest testing but did not perform any exercise intervention. After 2–3 wk of dietary acclimation and familiarization with the exercise hardware, protocols, and study procedures, subjects were confined to 70 d of 6° head-down tilt bed rest. Here, we present pre- and post-bed rest muscle, bone, and cardiovascular outcomes.

Exercise Training

Exercise prescription—Subjects performed aerobic exercise $6\text{ d}\cdot\text{wk}^{-1}$ and resistance exercise $3\text{ d}\cdot\text{wk}^{-1}$ using the “SPRINT” protocol. Briefly, aerobic exercise sessions consisted of alternating days of continuous cycle exercise for 30 min at 75% of $\dot{V}\text{O}_{2\text{peak}}$ ($3\text{ d}\cdot\text{wk}^{-1}$) with interval treadmill sessions of 30-s, 2-min, or 4-min intervals ($3\text{ d}\cdot\text{wk}^{-1}$) at nearly maximal intensity as previously described (9). Resistance exercise was performed on the

continuous aerobic days, and all training sessions were separated by at least 4 h to optimize bone growth (6). Resistance training consisted of three sets of each of four supine lifts (squat, leg press, unilateral leg curl, and heel raise); squats and leg press were each performed using a standard shoulder-width stance, single-leg stance, or wide-leg stance on a rotating basis. Training followed a nonlinear periodized model in which load and repetitions were varied on a daily basis to optimize adaptations (7,8). After 6 wk of training, the number of repetitions was decreased to allow for increased loading. The one exception was the supine squat “heavy” day, which was not adjusted to three repetitions after 6 wk and remained at five repetitions for the entire study due to subject safety concerns. At every resistance training session, the final set of each exercise was performed to muscle failure; loads for the subsequent training session were increased (or occasionally decreased) accordingly to provide an overload stimulus within the prescribed sets and repetitions. Supplemental Tables 1 and 2 provide a sample 10-wk exercise prescription (see Table, Supplemental Digital Content 1, Weekly Training Schedule, <http://links.lww.com/MSS/B236>, and Supplemental Digital Content 2, Program Variables for the Resistance Training Intervention, <http://links.lww.com/MSS/B237>). Supplemental Table 3 illustrates the integration of resistance exercise and aerobic exercise (see Table, Supplemental Digital Content 3, Integration of Aerobic and Resistance Showing Time Spent Exercising, <http://links.lww.com/MSS/B238>).

Exercise devices—Ex/ExT subjects used a suite of exercise hardware that allowed for an exercise variety and intensity that is similar to that available to ISS astronauts. All aerobic interval sessions were completed on the standalone zero-gravity locomotion simulator vertical treadmill, with subjects loaded to 75% to 80% of body weight. Continuous interval sessions were performed on a supine cycle ergometer. Resistance exercises were performed on horizontal squat, leg press, and leg curl machines. FLY subjects followed the same exercise prescription but with modifications based on the exercise equipment itself. All aerobic exercises were performed using seated rowing. Flywheel resistance training was slightly modified to achieve similar training stimulus. In particular, because it is not possible to perform squat exercise on the flywheel, the number of sets for each exercise was increased from 3 to 4. Flywheel subjects thus completed the same number of repetitions but with four sets of three exercises: leg press, heel raise, and leg curl. Subjects were instructed to perform maximal contractions on each repetition. The number of repetitions varied per the periodization schedule. The nature of flywheel training is such that progression naturally occurs as a consequence of the maximal nature of the exercise efforts.

Testosterone supplementation—Placebo or testosterone enanthate injections (100 mg·wk⁻¹, intramuscular) were administered in 2-wk intervals (i.e., weekly testosterone enanthate for 2 wk, followed by 2-wk off) for the duration of the 70-d bed rest period. Injections occurred immediately before bed rest on BR – 1, and during bed rest on BR7, BR28, BR35, BR56, and BR63.

Outcome Assessments

Adverse events monitoring/safety—All exercise training–related adverse events were monitored and reported on subject case report forms.

Exercise training attendance and prescription adherence—Attendance was calculated as the number of exercise sessions attended divided by the total number of planned sessions. Aerobic exercise intensity was monitored daily using continuous heart rate (HR) measurements, and metabolic intensity was measured during one session per week as described previously. Briefly, subjects were fitted with an HR monitor (Polar 810i; Polar USA Inc, Montvale, NJ) and a facemask connected to a metabolic cart (TrueOne 2400; ParvoMedics, Sandy, UT) before the start of one weekly exercise session. Baseline metabolic rate was established during a 10-min preexercise rest period, and metabolic data were collected throughout exercise and for 30 min after exercise.

Isokinetic leg strength—Knee and ankle extension/ flexion muscle strength were measured using an isokinetic dynamometer (Biodex System 4; Biodex Medical Systems, Shirley, NY) following the same protocol used by our group previously (5). Briefly, knee and ankle extensor/flexor peak torque production was assessed during maximal repetitions performed at $60^{\circ}\cdot\text{s}^{-1}$ and $30^{\circ}\cdot\text{s}^{-1}$, respectively.

Muscle performance—Lower body muscle performance was determined before and after bed rest using a leg press and bench press test battery recently developed in our laboratory (10). Modified and instrumented leg press and bench press stations were used to assess isometric strength and dynamic power as previously described (9). To measure upper and lower body isometric strength, subjects performed three maximal efforts for 5 s each with 30 s of rest between each effort. To assess upper and lower body dynamic power and work capacity, subjects performed 21 consecutive ballistic, concentric-only bench press, and bilateral leg press actions with the load fixed at 30% (bench press) and 40% (leg press) of the measured maximal isometric force, which has previously been shown to elicit maximal power output (10). A magnetic brake (Fitness Technology) was used to catch the weight as soon as the sled reached its peak height so that no eccentric muscle actions were performed. Power and total work were calculated (9).

Vertical jump—Subjects performed three maximal effort jumps with 60–90 s of rest between each jump. All jump trials were performed on a force plate, and data were acquired using a custom software program sampled at 1000 Hz (LabVIEW, National Instruments). Acceleration profile, jump height, peak acceleration, peak velocity, and peak power were calculated.

Muscle magnetic resonance imaging—CSA of the lower leg muscles was obtained from magnetic resonance imaging scans before and after bed rest. Images were acquired from the level of the ankle mortise to the iliac crest. The methods and reliability of this technique have been previously reported by our laboratory (11). Muscle CSA was manually traced using Image-J (National Institutes of Health, Bethesda, MD; version 1.42) (12).

Bone and body composition assessments—Body mass was obtained daily using a patient-lift bed scale. Dualenergy x-ray absorptiometry scans were obtained before, during, and after bed rest. Scans included whole-body and site-specific analysis of bone mineral density (BMD) at the legs, spine, and pelvis. Blood (bone-specific alkaline phosphatase

(BSAP), calcium, osteocalcin) and urine markers (calcium, deoxypyridinoline (DPD), and N-telopeptide) of bone formation and degradation were also obtained.

Maximal aerobic capacity and ventilatory threshold—Aerobic capacity ($\dot{V}O_{2\text{peak}}$) was assessed during upright peak cycle ergometry before and after the bed rest period. Ventilatory threshold (VT) was calculated from the data obtained during each peak cycle test. The peak cycle test and VT assessment methods are previously described (9,13).

Cardiac structure and function—Subjects underwent three-dimensional transthoracic imaging by use of a commercial ultrasound system (iE33; Phillips Healthcare) at least 12 h after the most recent exercise session. Images were obtained by a single, experienced sonographer according to the American Society of Echocardiography guidelines (14). A minimum of three consecutive cardiac cycles were measured and averaged. Left ventricular mass and volumes were obtained from three-dimensional imaging (15). Using the two-dimensional images, longitudinal strain was assessed using a dedicated software package (Q-Lab; Phillips Healthcare).

Statistical Analysis

Statistical analyses were conducted using Stata, IC software (v14.21) and setting two-tailed alpha to reject the null hypothesis at 0.05, with false-discovery adjustments following all hypothesis tests. Our experimental design is a mixed factorial, with repeated observations collected before and after 70 d of bed rest among subjects randomized to one of four different groups described earlier (CONT, EX, ExT, FLY). Multiple pre-bed rest blood (BR – 12, BR – 2) and urine (BR – 10, BR – 9, BR – 6, BR – 5) time points were averaged. We evaluated the effects of condition (CONT, EX, ExT, FLY) and bed rest (pre/post) in separate mixed-effects models per dependent variable, with *a priori* simple interaction terms comparing the pre/post changes among all possible pairs of condition (CONT vs EX, CONT vs ExT, CONT vs FLY, EX vs ExT, EX vs FLY, and ExT vs FLY). Each of these models included a random Y-intercept to accommodate the within-subject experimental design. Each statistical test also underwent a rigorous examination of the distribution of model residuals before hypothesis testing, and although nearly all of our analyses were satisfactorily evaluated without data transformations, overly influential outliers, or model adjustments, it was necessary to use the natural-log transformation of two of our outcomes to meet model assumptions (BSAP, DPD) and the elimination of one (out of 68) of the BSAP observations that remained a statistical outlier after this transformation. Because of the large number of outcomes and statistical comparisons within outcome, we adjusted our significance testing *P* values using a 10% false discovery rate adjustment (16).

RESULTS

Subject recruitment took place between May 2011 and August 2014. A total of 10,142 subjects were screened. Of these, 110 met inclusion criteria, 62 passed phase I screening, and 45 passed minimum fitness requirements and agreed to participate. Of these, 39 were randomized and 34 (CONT: $n = 8$, 37 ± 8 yr, 79 ± 10 kg; EX: $n = 9$, 33 ± 10 yr, 77 ± 14 kg; ExT: $n = 8$, 34 ± 6 yr, 76 ± 7 yr; FLY: $n = 8$, 29 ± 5 yr, 77 ± 14 kg) completed study

procedures. One female subject completed the study before implementation of the randomized double-blind procedures for the testosterone group was added; thereafter, male subjects were enrolled.

Safety data

Bed rest–related adverse included headaches, nasal stuffiness, and nerve irritation after muscle biopsy (4). Seven exercise training–related adverse events were observed consisting of muscle strain ($n = 2$), heel pain ($n = 1$), foot edema ($n = 1$), and ear infection ($n = 3$). Ear infections were attributed to sweat in the ear during supine exercise.

Exercise prescription attendance and adherence

Overall attendance to planned exercise sessions was 100%; all missed exercise sessions were rescheduled and no sessions were lost. Adherence to resistance exercise was excellent as evaluated by resistance loads (Table 1). Aerobic exercise adherence based on HR was excellent; however, $\dot{V}O_2$ targets for interval and continuous exercise were lower than prescribed (Table 2).

Muscle strength

Muscle strength and endurance data are shown in Table 3. Significant interaction effects between the CONT group and all EX groups were observed for leg press total work, isokinetic upper and lower leg strength, and vertical jump power and maximal jump height. Significant interaction effects between CONT and traditional exercise were also observed in leg press maximal power and isokinetic strength.

Muscle magnetic resonance imaging

After 70 d of head-down tilt bed rest, loss of quadriceps and soleus muscle CSA was significantly attenuated by exercise countermeasures (Table 4). Significant interaction effects between the CONT group and all EX groups were observed for quadriceps and soleus CSA.

Bone and body composition

Body mass was maintained within 2% of the pre–bed rest in all groups as designed (pre–bed rest body weight, ExT: 77.61 ± 14.4 kg; EX: 88.64 ± 6.75 kg; FLY: 78.03 ± 13.66 kg; CONT: 77.01 ± 10.78 kg). Significant interaction effects were observed for body composition where CONT experienced an unfavorable change in body composition (12.4% $\pm$ 15.2% increase in fat mass (FM), 4.1% $\pm$ 5.2% decrease in fat-free mass (FFM)), whereas EX increased FM (7.0% $\pm$ 4.9%) and maintained FFM (–0.9% $\pm$ 2.9%), ExT showed an improvement in body composition (4.4% $\pm$ 3.4% increase in FFM, 2.7% $\pm$ 11.1% decrease in FM), and FLY decreased FM (–3.9% $\pm$ 8.5%) and maintained FFM (–0.9% $\pm$ 2.1%). Total body, leg, spine, and pelvis BMD were maintained in all groups during 70 d of bed rest. There were no group interactions in bone blood or urine markers, with the exception of urine calcium (Table 5).

Maximal aerobic capacity and VT

Maximal aerobic fitness and VT data are shown in Table 6. Significant interaction effects between the CONT group and all exercise groups were observed for $\dot{V}O_{2peak}$, VT, and peak watts. $\dot{V}O_{2peak}$ was maintained from pre- to post-bed rest in all exercise groups similarly, whereas significant declines were observed in CONT in $\dot{V}O_{2peak}$ (~10%). A similar trend was observed for VT where exercise groups maintained from pre- to post-bed rest and CONT declined (~14%).

Cardiac structure and function

There were no significant differences between groups in cardiac function or morphology (left ventricular mass, CONT: 143.8 ± 19.6 g vs 124.4 ± 18.8 g; ExT: 157.8 ± 22.3 g vs 145.6 ± 15.1 g; EX: 152.4 ± 17.4 g vs 143.3 ± 12.7 g; FLY: 121.6 ± 23.2 g vs 110.6 ± 22.6 g).

DISCUSSION

This study is particularly novel because of its long duration (70 d of unloading) and its comprehensive, multisystem scope in terms of both the exercise prescriptions and the outcome variables. Three different whole-body comprehensive exercise countermeasure strategies were directly compared and outcomes assessed covering key physical performance variables such as aerobic capacity, muscle strength, and power as well as key physiologic variables related to cardiovascular, muscle, and bone health. Although it may seem logical that exercise should be able to prevent deconditioning during unloading, most research studies focused very narrowly on a single-organ system for both training and assessment. Furthermore, the details of how exercise should be prescribed (mode, intensity, duration, frequency) and how aerobic and resistance exercise should be integrated together to protect the entire body have not been evaluated during long-duration unloading. The SPRINT exercise prescription was developed after a comprehensive evidence-based assessment of NASA spaceflight data and published literature from spaceflight, spaceflight analogs, and ground-based exercise training. The resultant SPRINT exercise prescription is a culmination of decades of research and spaceflight experience. In this bed rest study, SPRINT was evaluated alone using ISS-like traditional exercise equipment and with low-dose testosterone as a potential supplement to enhance the effectiveness of training. With an eye to the future of very long-duration exploration spaceflight where resources will likely be highly constrained, the SPRINT exercise prescription was also testing using a single smaller exercise device that provides both aerobic and resistance exercise.

The principal new findings from this study are that 1) the SPRINT exercise protocol (a nonlinear program incorporating carefully timed high-intensity aerobic and resistance exercise) with traditional exercise equipment alone and with the addition of low-dose testosterone supplementation was safe and abrogates multisystem deconditioning, and 2) FLY training was effective in mitigating multisystem deconditioning relative to the exercise performed on traditional (e.g., resistance machines, treadmill, cycle ergometer) exercise equipment. This is the first trial to directly compare the safety and effectiveness of a suite of

exercise devices with or without testosterone supplementation with a single resistance and aerobic exercise device. Overall, our findings have important implications for the design and implementation of exercise-based countermeasures on future long-duration spaceflight missions. In particular, this study suggests that the SPRINT exercise protocol has excellent potential to mitigate cardiovascular and skeletal muscle health and performance sufficiently (within the NASA standards) during long-duration spaceflight. Furthermore, there are several ways such mitigation may be realized, with traditional exercise equipment with or without testosterone or with a compact rowing/resistance exercise device. The fact that the SPRINT exercise prescription was an effective countermeasure when implemented using different exercise hardware is an important finding.

Exercise safety

We observed a total of seven exercise-training related adverse events. This low number of events in 2070 exercise sessions (0.3%) is likely the results of several mechanisms in place to ensure subject safety: 1) exercise subjects completed a 3-wk pre-bed rest familiarization period in which research team members instructed subjects on proper and safe execution of the exercises; 2) pre-bed rest resistance exercise training sessions were initially performed under light load with a focus on the proper form for each exercise; 3) subjects were evaluated on supine resistance exercise loads to obtain 3, 5, 8, and 12 repetition maximum values immediately before initiating bed rest; 4) subjects were instructed on proper running or rowing form and were introduced to the three interval protocols throughout familiarization sessions; and 5) due to the unique exercise equipment (5), all exercises were performed under the supervision of two exercise physiologists. Together, these steps helped to ensure that subjects were comfortable and able to perform the SPRINT prescription the first day of bed rest and minimized injury risk.

Exercise prescription

Previous bed rest studies incorporating exercise have based aerobic and resistance training at moderate-intensities (50%–75% of a predetermined physiological parameter, typically age-predicted HR maximum, or 1 repetition maximum) (17,18). In addition to doubling the duration of bed rest compared with previous work, the exercise prescription in this study was also unique. The basis of the SPRINT exercise prescription is an undulating periodization protocol for both resistance and aerobic exercises. Three intensities of resistance and aerobic training sessions were used and rotated among various exercises and days (see Table, Supplemental Digital Content 1, Weekly Training Schedule, <http://links.lww.com/MSS/B236>). This undulating scheme served several purposes: 1) provided diverse loading stimuli to the bone and muscle, 2) reduced training plateaus and staleness, 3) allowed for attaining higher training intensities, and 4) attempted to minimize overuse injury by optimizing exercise duration and repetitions. Collectively, the SPRINT exercise prescription clearly demonstrates the potential benefit of high-load resistance exercise coupled with high-intensity interval training using conventional and novel equipment in spaceflight.

Exercise adherence

All subjects successfully adhered to the novel, high-intensity integrated aerobic and resistance training program. Specifically, the nonlinear resistance training program

incorporating heavy loads was effectively performed by all subjects (Table 1), indicating that resistance exercise can be performed in the supine position using traditional and flywheel-based exercise equipment. Moreover, all subjects achieved prescribed HR during aerobic training sessions. This investigation was the first to assess $\dot{V}O_2$ weekly during training sessions to further evaluate adherence. Interestingly, despite achieving prescribed HR, $\dot{V}O_2$ was lower than expected, particularly in the traditional exercise group (Table 2). The lower $\dot{V}O_2$ observed in the traditional exercise group could be due to the exercise modality, lower exercise stroke volume, or lower muscle perfusion. Supine cycle ergometry and horizontal treadmill running primarily used lower body muscles, whereas rowing is a fully body activity. Alternatively, previous studies demonstrated that exercise performance is impaired in a supine posture when compared with an upright posture, which has primarily been attributed to differences in muscle perfusion (19). For instance, gravity adds approximately 25 mm Hg of perfusion pressure to the arterial and venous vessels of the quadriceps muscles at rest in the upright posture (9). Absence of the gravity-induced hydrostatic pressure component in the supine posture results in a lower perfusion pressure (20,21). During exercise, the muscle pump increases the arteriovenous pressure difference across the active muscle due to the venous pressure being reduced close to zero during each relaxation cycle (9). However, the change in arteriovenous pressure is lower in a supine posture primarily due to the absence of the arterial hydrostatic pressure component (20). To this end, Egana et al. (22) demonstrated that there were slowed $\dot{V}O_2$ kinetics in the supine posture, suggesting inadequate perfusion of, and oxygen delivery to, exercising muscle. Therefore, the combined decrease in arterial perfusion pressure and the lack of an effective muscle pump in the supine position may contribute to a lower $\dot{V}O_2$ during supine submaximal exercise. Future work examining macrocirculation (i.e., blood flow in large arteries) and microcirculation (i.e., perfusion) could provide crucial information regarding limitations to exercise in acute microgravity.

Exercise efficacy

Despite following a shorter exercise regimen than previous studies, exercise of approximately only 1 h·d⁻¹ preserved muscle, cardiovascular, and bone after 70 d of bed rest. Previous bed rest studies have fully or partially protected muscle strength and BMD with either a free weight exercise training regimen over a relatively short period of unloading (23) or maximal inertial flywheel exercise or resistance vibration exercise over a longer bed rest duration (>50 d) (24–27). Similarly, studies using aerobic exercise training over short- and long-duration bed rest have shown that cardiac function and upright $\dot{V}O_{2peak}$ is protected (17,18,28,29). To our knowledge, we are the first not only to report wholesale preservation of multisystem function using resistance, treadmill, and cycle exercise devices over a prolonged bed rest duration, but also to concurrently obtain similar results with an inertial flywheel device. Thus, the protective effect can probably be largely attributed to the exercise prescription itself because muscle, cardiac, bone, and $\dot{V}O_{2peak}$ preservation was similar between all exercise groups. These findings provide critical information for future exploration spaceflight missions. First, the SPRINT exercise prescription, which requires less time than historic ISS training programs, effectively maintained multisystem function

with a suite of exercise equipment designed to mimic exercises that can be performed on the ISS. Second, adaptation of the same prescription to training with a single, small inertial flywheel resulted in similar outcomes, suggesting that such a prescription may be effective on exploration-class missions that will not have the volume or vehicle power to support large or multiple exercise devices such as those on the ISS. The well-documented efficacy of inertial flywheels to protect skeletal muscle in bed rest and other unloading models should position it as a leading candidate for use in volume-constrained spaceflight where aerobic and resistance exercise modalities need to be available in a single device.

Limitations

There are several limitations that should be considered. The effectiveness of the SPRINT exercise prescription in bed rest may be not directly translated to spaceflight for a variety of reasons. First, although the biomechanics of running is likely similar in spaceflight and on the ground (30), the weight-lifting biomechanics is not (unpublished observations). Astronauts on ISS are often limited by the load they can handle at the back during resistance training sessions rather than their leg strength due to the biomechanics of ARED. In addition, other aspects of the ISS environment were not simulated during the bed rest study; this includes a wide variety of factors such as the relatively high-sodium diet lacking fresh foods, a demanding work schedule, disruptions to circadian rhythm and sleep cycles, social isolation, radiation exposure, and others.

The SPRINT protocol or bed rest alone did not have a significant effect on BMD or molecular markers of BMD. This could be because 70 d was too short to see statistically significant effects. Although bed rest eliminates the daily bone loading stimulus associated with normal ambulation, the presence of gravity even in the supine posture likely mitigates some of the loss in bone observed during complete unloading such as spaceflight. The effectiveness of the SPRINT prescription on bone may be different during spaceflight because of complete absence of gravity and the longer-duration exposures of unloading with ISS and exploration class missions. There was some occasional in-bed rest testing, and this coupled with the ~3% precision error of dual-energy x-ray absorptiometry scanning may have been enough to obscure the small declines in BMD that would be expected with 70 d of bed rest in control subjects. The SPRINT exercise research program is currently in evaluation on the ISS and will provide more definitive results for bone.

In this bed rest study, we did not detect any additional training-related benefit of the low-dose testosterone supplementation. However, given that none of the bed rest subjects started the study with low testosterone levels, testosterone may be advantageous for older astronauts, those with low testosterone levels, or those unable to perform SPRINT exercise (see companion paper for details) (31).

CONCLUSIONS

The SPRINT program incorporating high-intensity resistance and aerobic exercise training is a safe countermeasure associated with mitigated bed rest-induced declines in muscle, bone (urine calcium), and cardiac morphology and function. The SPRINT prescription was effective when using a suite of exercise hardware similar to that currently available to

astronauts onboard the ISS and a single resistance and aerobic flywheel-based device, suggesting that the SPRINT prescription could be used on future exploration missions in volume-constrained vehicles.

Exercise is medicine

This work also forms the basis for the eventual development of physical rehabilitation programs to combat hospital-based deconditioning. Although most clinical populations could not perform at the high intensities used in this study, these data show that only 1 h·d⁻¹ of exercise is capable of counteracting 23 h·d⁻¹ of strict bed rest. No medications exist with this level of effectiveness against muscle wasting and cardiovascular deconditioning. It is likely that variants to the SPRINT exercise program that are based on the SPRINT training principles could be an effective treatment for hospital-based deconditioning as well. Although exercise is widely implemented in some clinical setting such a rehabilitation medicine, it has not yet been fully embraced in other areas such as intensive care or pregnancy-induced bed rest. SPRINT may also be a viable strategy for prehabilitation before elective medical procedures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1.

Average load (kg) on traditional equipment during bed rest.

	Week1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
Standard squat	102.3 ± 14.1	110.5 ± 16.4	120 ± 22.7	113.6 ± 15.9	116.4 ± 22.7	131.4 ± 24.1	112.3 ± 26.8	131.4 ± 13.2	122.7 ± 48.2	600.6 ± 25
Wide squat	105.5 ± 18.2	111.4 ± 16.4	120 ± 18.6	113.2 ± 23.6	121.4 ± 19.1	124.6 ± 15.9	132.3 ± 24.1	140.5 ± 19.1	125.9 ± 123	530.2 ± 31.4
Single-leg squat	61.4 ± 10.5	60.5 ± 12.3	75.5 ± 11.4	68.6 ± 12.3	77.7 ± 11.8	85.5 ± 10	72.3 ± 15.9	81.8 ± 10.5	79.1 ± 15	367.4 ± 16.4
Standard leg press	112.8 ± 17.8	112.7 ± 17.7	126.4 ± 20	123.2 ± 22.7	127.3 ± 17.3	130 ± 19.1	136.4 ± 18.6	140.5 ± 15.9	122.3 ± 15.9	653.4 ± 20.9
Wide-leg press	109.1 ± 19.1	115 ± 22.3	130.5 ± 18.6	118.2 ± 15.9	127.7 ± 18.6	141.8 ± 15	124.1 ± 20.5	140 ± 17.7	141.4 ± 15.9	613.8 ± 21.8
Single-leg press	66.4 ± 6.9	68.6 ± 13.2	77.7 ± 10.5	66.8 ± 8.6	77.7 ± 11.8	84.1 ± 11.8	81.4 ± 12.3	85 ± 15	88.6 ± 10.5	358.6 ± 21.4
Leg curl	22.3 ± 6.0	24.1 ± 6.8	28.6 ± 8.6	25.9 ± 7.3	28.2 ± 8.2	31.8 ± 9.1	28.6 ± 8.6	32.3 ± 9.6	32.3 ± 10.5	134.2 ± 9.1
Heel raise	131.4 ± 12.3	137.7 ± 15.9	153.2 ± 17.3	143.6 ± 19.1	150.9 ± 19.6	163.2 ± 24.6	151.4 ± 26.8	164.6 ± 25.5	157.3 ± 30.9	730.4 ± 27.3

TABLE 2.

Aerobic exercise during bed rest (mean $\pm$ SD).

	EX			ExT			FLY		
	% $\dot{V}O_{2peak}$	% Peak HR	% $\dot{V}O_{2peak}$	% Peak HR	% $\dot{V}O_{2peak}$	% Peak HR	% $\dot{V}O_{2peak}$	% Peak HR	% $\dot{V}O_{2peak}$
4-min interval	72 $\pm$ 10	89 $\pm$ 12	71 $\pm$ 9	89 $\pm$ 6	82 $\pm$ 8	95 $\pm$ 3			
2-min interval	73 $\pm$ 11	88 $\pm$ 10	70 $\pm$ 13	90 $\pm$ 4	83 $\pm$ 8	96 $\pm$ 4			
30-min continuous	70 $\pm$ 8	85 $\pm$ 4	63 $\pm$ 5	83 $\pm$ 4	69 $\pm$ 7	88 $\pm$ 4			

Aerobic data represent the average intensity during the working phases of the 2- and 4-min intervals, and the 30-min continuous exercise and the average intensity across the entire continuous session.

TABLE 3.

Muscle strength and endurance.

	CONT			Ex			Ext			FLY		
	BR - 5	BR + 0	BR - 5	BR + 0	BR - 5	BR + 0	BR - 5	BR + 0	BR - 5	BR + 0	BR - 5	BR + 0
Leg press MIF, N	1975 ± 578	1657 ± 728	2070 ± 406	1965 ± 533	1857 ± 300	1768 ± 258	2367 ± 633	2196 ± 587				
Leg press total work, J	8616 ± 1942	6714 ± 1241	8644 ± 2377	8162 ± 2450 *	8571 ± 1744	8137 ± 1744 *	10130 ± 2351	9409 ± 2228 *				
Leg press max power, W	1836 ± 430	1445 ± 342	1943 ± 436	1830 ± 581 *	1791 ± 249	1724 ± 316 *	2377 ± 721	2194 ± 609				
Isokinetic KE 60	191.4 ± 45.0	147.7 ± 42.0	201.0 ± 59.6	184.9 ± 64.2 *	206.1 ± 32.3	197.7 ± 26.8 *	212.7 ± 36.6	185.0 ± 32.5 **				
Isokinetic PF 30	126.3 ± 32.0	89.3 ± 16.5	129.5 ± 39.4	116.3 ± 31.0	136.6 ± 20.5	118.9 ± 22.3	109.6 ± 19.0	104.8 ± 23.6 *				
Vertical jump max height, cm	42.5 ± 7.0	32 ± 5.8	43.6 ± 5.4	41.4 ± 5.5 *	44.3 ± 8.2	39.3 ± 6.8	45.5 ± 4.2	44 ± 5.2 *				
Vertical jump max power, W kg ⁻¹	44.6 ± 5.8	36.5 ± 4	45.5 ± 5.8	43.8 ± 6.7 *	46.0 ± 6.9	44.1 ± 8 *	50.3 ± 6.2	49.5 ± 6.8 *				

Values are expressed as means ± SD.

* $P < 0.003$, group-time Interaction versus CONT.

** $P < 0.003$, group-time Interaction versus Ex.

BR - 5, 5 d before the start of bed rest; BR + 0, the day bed rest is completed; MIF, maximal isometric force; KE, knee extension; PF, plantar flexor.

TABLE 4.

Muscle CSA.

	CONT			EX			Ext			FLY		
	BR - 5	BR + 0		BR - 5	BR + 0		BR - 5	BR + 0		BR - 5	BR + 0	
Quadriceps, cm ²	75.3 ± 17.7	68.1 ± 15.9		78.7 ± 10.7	81.1 ± 12.1 *		71.6 ± 11.6	75.0 ± 12.6 *		86.4 ± 16.0	84.6 ± 18.4 **, **	
Hamstrings, cm ²	35.6 ± 7.2	31.6 ± 8.2		32.5 ± 4.3	32.8 ± 5.4 *		32.3 ± 4.9	32.8 ± 5.0 *		38.0 ± 9.4	35.9 ± 7.9	
Soleus, cm ²	23.6 ± 5.2	18.0 ± 3.8		24.4 ± 3.0	22.2 ± 2.4 *		23.7 ± 2.9	21.7 ± 3.0 *		26.8 ± 3.7	24.2 ± 3.5 *	

Values are expressed as means ± SD.

* $P < 0.003$, group-time interaction versus CONT.

** $P < 0.003$, group-time interaction versus Ext.

BR - 5, 5 d before the start of bed rest; BR + 0, the day bed rest is completed.

TABLE 5.

Rone blood and urine markers.

	CONT		EX		ExT		FLY	
	BR - 5	BR + 0	BR - 5	BR + 0	BR - 5	BR + 0	BR - 5	BR + 0
Blood BSAP, U·L ⁻¹	28 ± 5	31 ± 7	24 ± 6	35 ± 16	33 ± 9	41 ± 10	31 ± 10	36 ± 11
Blood calcium, mmol·L ⁻¹	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1
Blood osteocalcin, ng·mL ⁻¹	26 ± 11	27 ± 11	29 ± 6	36 ± 9	28 ± 8	34 ± 10	28 ± 7	30 ± 6
Urine calcium, mmol·d ⁻¹	6.7 ± 2.3	7.9 ± 2.7	6.3 ± 3.0	4.8 ± 1.6	6.2 ± 3.2	5.8 ± 3.5 [*]	4.9 ± 2.4	5.3 ± 1.9 ^{**}
Urine DPD, nmol·d ⁻¹	45 ± 10	84 ± 28	62 ± 16	85 ± 28	50 ± 19	87 ± 21	44 ± 14	62 ± 13
Urine NTX, nmol·d ⁻¹	393 ± 156	518 ± 192	429 ± 125	639 ± 192	492 ± 201	596 ± 172	647 ± 216	868 ± 283

Values are expressed as means ± SD.

^{*} $P < 0.003$, group-time interaction versus CONT.

^{**} $P < 0.003$, group-time interaction versus ExT.

BR - 5, 5 d before the start of bed rest; BR + 0, the day bed rest is completed; NTX, N-telopeptide.

TABLE 6.

Peak cycle.

	CONT			EX			ExT			FLY		
	BR - 5	BR + 0	BR - 5	BR - 5	BR + 0	BR - 5	BR - 5	BR + 0	BR - 5	BR - 5	BR + 0	BR + 0
$\dot{V}O_{2peak}$, L·min ⁻¹	2.9 ± 0.6	2.2 ± 0.4	3.2 ± 0.6	3.2 ± 0.6	3.2 ± 0.6*	3.2 ± 0.5	3.1 ± 0.4*	3.1 ± 0.4*	3.2 ± 0.7	3.0 ± 0.6*		
VT, L·min ⁻¹	2.0 ± 0.4	1.5 ± 0.3	2.0 ± 0.3	2.0 ± 0.4*	2.1 ± 0.4	2.0 ± 0.4*	2.0 ± 0.4*	2.0 ± 0.5	2.0 ± 0.5	2.0 ± 0.5*		
Peak workload, W	242 ± 53	181 ± 42	261 ± 47	265 ± 53*	267 ± 28	264 ± 25*	272 ± 53	264 ± 32*	272 ± 53	264 ± 32*		
Peak HR, bpm	189 ± 7	188 ± 10	177 ± 8	176 ± 10	178 ± 14	178 ± 9	182 ± 5	186 ± 8	182 ± 5	186 ± 8		

Values are expressed as means ± SD.

* $P < 0.003$, group-time interaction versus CONT.

BR - 5, 5 d before the start of bed rest; BR + 0, the day bed rest is completed.