Blood Flow Restricted Exercise Compared to High Load Resistance Exercise During Unloading

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BACKGROUND: Bed rest studies have shown that high load (HL) resistance training can mitigate the loss of muscle size and strength during musculoskeletal unloading; however, not all individuals are able to perform HL resistance exercise. Blood flow restricted (BFR) resistance exercise may be a novel way to prevent maladaptation to unloading without requiring HL exercise equipment. This study evaluated the muscular training adaptations to HL and BFR resistance training during unilateral lower limb suspension (ULLS), a human limb unloading model. ULLS allows for evaluation of exercise training in both weight-bearing and nonweight-bearing legs within the same individual.

METHODS: There were 13 participants who completed 25 d of ULLS and were counterbalanced to: 1) HL, $N = 6$; or 2) BFR, $N = 7$, training groups. During ULLS, HL and BFR performed unilateral leg press and heel raise exercise (3 d/wk).

RESULTS: In weight-bearing legs, both HL and BFR increased knee extensor muscle cross-sectional area (CSA) and strength. In nonweight-bearing legs, knee extensor CSA and strength increased only in HL and decreased with BFR.

CONCLUSION: HL and BFR resistance exercise were both effective exercise programs for the weight-bearing leg. However, BFR exercise was not as effective as HL resistance exercise in the nonweight-bearing leg. These data show that exercise that improved muscle CSA and strength in ambulatory weight-bearing conditions was not sufficient to maintain muscle function during unloading. For the preservation of muscle CSA and strength, BFR exercise should be considered an adjunct but not a primary exercise countermeasure for future space missions.

KEYWORDS: exercise countermeasures, spaceflight, ULLS, anabolic Impairment.

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The absence of daily weight-bearing during prolonged bed rest, unilateral lower-limb suspension (ULLS), and microgravity exposure during spaceflight results in the loss of skeletal muscle cross-sectional area (CSA) and function.[14,17] For future spaceflight missions beyond low-Earth orbit, reductions in muscular health could prevent astronauts from successfully performing critical mission tasks (e.g., unassisted exit from a vehicle in a space suit) and increase the time needed to complete exploration or construction tasks. Exercise performed during transit remains the primary countermeasure for attenuating loss of muscular health during space exploration. Performing traditional resistance exercises and increasing the loading capability of equipment used in space has been the primary focus of exercise in space on the International Space Station (ISS).[18] It is possible that crewmembers may not always be able to perform high load exercise as a result of deconditioning, injury, or equipment limitations in the future, yet to be designed Mars transit vehicles. An alternative approach to performing high-load (HL) resistance exercise could be to perform low-load blood flow restricted (BFR) exercise.[19] BFR exercise incorporates resistance exercise at lower loads when combined with an external inflation cuff. This type of exercise training can potentially be performed on equipment with lower loading capability given it uses hypoxia to increase metabolic stress. Previous studies suggest both HL and BFR can significantly improve muscle CSA and strength during normal

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ambulation[5,26,27] and attenuate losses in muscle CSA and strength during disuse compared to nonexercise controls.[1,8] However, a direct comparison of HL and BFR exercise countermeasures during unloading has not been performed.

Evidence also suggests that the anabolic response to stimuli may be blunted during unloading or disuse conditions (i.e., anabolic impairment),[12,16] prompting the need to also compare the relative effectiveness of these exercise countermeasures during both weight bearing and nonweight bearing. It is critical for resistance exercise programming to be able to overcome unloading-induced anabolic impairment in order to optimize exercise devices and exercise prescriptions for future missions beyond low Earth orbit. It cannot be assumed that a training program that is effective with ambulatory subjects would be equally effective under unloaded conditions. In addition to the benefit to the astronaut population, this information could help improve health outcomes in patients requiring long-duration bed rest or other disuse conditions. Therefore, this study examined the muscular exercise training adaptations from HL and BFR resistance exercise training during weight bearing and nonweight bearing. Given the success of both resistance exercise techniques,[1,5,8] it was hypothesized that BFR exercise and HL resistance exercise would result in similar muscular training adaptations in weight-bearing limbs; however, these adaptations would be dampened relative to the same exercise training in nonweight-bearing limbs.

METHODS

Subjects

This study protocol was approved in advance by Institutional Review Boards at NASA Johnson Space Center, and Institutional Ethical Review Boards from Syracuse University and the University of Houston. Each subject provided written consent before participating. Thirteen participants volunteered and were medically cleared for the investigation by the Human Test Subject Facility at NASA Lyndon B. Johnson Space Center. Inclusion in the study was contingent upon passing a modified Air Force Class III physical that included: an electrocardiogram, urinalysis, blood chemistry profile, tests for vision and hearing, drug and alcohol screening, and a pregnancy test when applicable. All subjects were free of any pre-existing musculoskeletal injury or disease. Subjects were excluded from the study if they had a history of blood clotting disorders or had allergies or sensitivities to milk proteins.

ULLS was the ground-based human unloading analogue selected for this investigation as it has previously demonstrated similar reductions in muscle mass and strength as bed rest and provides a unique opportunity to study both nonweight-bearing and weight-bearing limbs within the same participant.[17] Subjects performed all ambulatory activity on crutches for 25 d while wearing a shoe with a 10-cm sole on the right foot. This eliminated ground contact by the left foot, thereby unloading the left lower limb. The right limb continued to have ground contact and remained weight-bearing throughout the ULLS period.[17] To mitigate the risk of a deep venous thrombosis in the nonweight-bearing limb,[3] subjects were encouraged to wear graduated compression stockings (Jobst Relief Therapeutic, BSN Medical Inc, Charlotte, NC), performed passive range of motion exercises for the knee and ankle twice per day, and to elevate their left leg whenever possible. To ensure compliance with ULLS, researchers had daily communication with subjects and performed skin temperature measurements of the legs during visits to the laboratory.[17] In addition, a planar accelerometer (AMP 331, Dynastream Innovations, Alberta, Canada) was worn before and during ULLS to allow for quantification of steps per day in the nonweight-bearing limb.[9]

Before the ULLS period, subjects completed an ambulatory control phase where five acute exercise sessions were performed.[11] After the control phase, all participants were counterbalanced by age and gender to: 1) high-load resistance exercise (HL, $N = 6$, 2 men, 4 women, mean ± SD: 33.8 ± 13.8 yr, 70.2 ± 17.0 kg, 168.3 ± 12.9 cm); or 2) blood flow restricted exercise (BFR, $N = 7$, 3 men, 4 women, 30.1 ± 12.1 yr, 66.7 ± 6.7 kg, 169.8 ± 12.2 cm). Muscle CSA, strength, and endurance data from the upper and lower legs were obtained the week prior to starting ULLS (Pre-ULLS) and on either day 24 or 25 of ULLS (Post-ULLS).

In the pre-ULLS ambulatory phase, participants were educated in food documentation, including serving sizes and accurate record keeping. To document food mass, each participant was also provided with a food scale (Taylor Precision Product, Oak Brook, IL). Participants kept records of their daily food intake for 3 to 5 d/wk pre-ULLS and during ULLS. To encourage any potential anabolic benefits from protein timing,[20] both BFR and HL consumed 240 ml of milk (Horizon, Organic Chocolate Reduced Fat Milk, Boulder, CO) immediately (<10 min) before and after each exercise session during ULLS in the presence of a member of the investigative team. Chocolate milk was used to increase palatability and could be available on the ISS or for future missions. The total amount of milk consumed (480 ml divided into 240-ml doses pre- and postexercise) contained 1506 kJ (360 kcal), 10 g total fat, 54 g carbohydrates, and 16 g protein total. Based on Moore et al.,[20] this dosage of protein was expected to facilitate an increased muscle protein synthesis in the postexercise period when combined with resistance exercise. Food records were analyzed post-ULLS for total energy intake and macronutrient composition using nutritional analysis software (Food Processor SQL, Esha Research, Salem, OR). Body mass was evaluated before exercise sessions using a calibrated laboratory scale (Detecto, Webb City, MO) once pre-ULLS and once per week during ULLS.

Equipment

HL and BFR performed three sets of supine, unilateral leg press and plantar flexion exercise on the Agaton Fitness System® (Agaton Fitness AB, Boden, Sweden) 3 d/wk. Light stretching of the legs in the supine position was allowed prior to each BFR and HL session, but no standard warm-up was implemented given the difficulty matching any potential work performed between the two groups. Compression stockings worn on the nonweight-bearing limb were removed during exercise sessions. Leg press was performed with the hip and knee at 90° flexion. Plantar flexion was performed with the hip at 0° and the knee at ~5° of flexion. HL exercised at an intensity between 70–80% of 1 repetition maximum (RM; obtained pre-ULLS) with 90 s rest between sets. BFR exercised at an intensity between 20–30% of 1 RM with continuous pressure (1.3 × supine systolic blood pressure; 140 ± 10 mmHg) applied by an electronic inflation system and a 6 × 83 cm cuff (E20 Rapid Cuff Inflator, D.E. Hokanson, Inc., Bellevue, WA). For the leg press, the cuff was placed on the proximal thigh.[8] For plantar flexion, the cuff was placed on the distal thigh. Between sets 90 s of rest was provided and the cuff remained inflated during all rest intervals. During each set, both HL and BFR performed as many repetitions as possible to volitional fatigue.[8] Exercise sessions during ULLS alternated which limb (nonweight-bearing or weight-bearing) would be trained first; however, leg press exercise for both legs was always performed prior to plantar flexion exercise.

Procedures

Muscle CSA of the nonweight-bearing and weight-bearing upper and lower leg muscles were obtained from MRI scans using a Signa Horizon LX 1.5T (GE Healthcare, Wauwatosa, WI). Prior to scanning, subjects rested supine for 30 min and were transferred to the MRI in the supine position to standardize for fluid shifts.[7] Images of both thighs and lower legs were generated using a repetition time of 2000 ms, echo time of 51 ms, slice thickness of 10 mm, and a gap between slices of 0 mm. All DICOM images were transferred to a computer for calculation of muscle CSA (cm^2) using the National Institutes of Health Image J software (U.S. National Institutes of Health, Bethesda, MD).[23] For each axial slice (from the appearance of the rectus femoris to the appearance of the gluteus maximus), the rectus femoris and grouped vasti (vastal lateralis, vaster medialis, vastus intermedius) were traced and analyzed. The rectus femoris and grouped vasti muscles were added together to represent the knee extensors. In the lower leg, the lateral gastrocnemius, medial gastrocnemius, and soleus were traced and analyzed on each axial slice (from the appearance of the lateral gastrocnemius to the slice where the lateral and medial gastrocnemius muscles were no longer distinguishable). The plantar flexors were defined as the sum of all three of the lower leg muscles traced. The same numbers of slices were measured for each subject and at each of the testing time points. The same investigator analyzed each individual muscle/group in duplicate (with the mean used as the CSA for analysis). Within-measurement reliability (measurement 1 vs. 2) for the knee extensors and plantar flexors CSA were 0.004% (0.2 cm^2) and 0.001% (0.04 cm^2), respectively.

Determination of unilateral 1-RM strength of both nonweight-bearing and weight-bearing knee extensors and plantar flexors muscle groups was performed on the Agaton Fitness System using the hip and knee position previously described for the leg press and plantar flexor exercises. Subjects performed a warm-up of 10 dynamic repetitions at a light to moderate weight. Then single attempts at progressively heavier weights were performed until 1 RM (the heaviest weight that could be

Table I. Leg Press and Plantar Flexion Exercise Prescriptions.

	WEIGHT-BEARING			NONWEIGHT-BEARING		
	HL	**BFR**	***t*-SCORE (*P*-VALUE)**	**HL**	**BFR**	***t*-SCORE (*P*-VALUE)**
Leg Press						
Load (kg)	40.3 ± 21.5	11.8 ± 4.0*	-3.459 (0.005)	40.1 ± 18.4	11.5 ± 3.7*	-4.040 (0.002)
Total Reps (#)	43 ± 12	54 ± 22	1.114 (0.289)	40 ± 16	47 ± 13	0.889 (0.393)
Set 1 Reps (#)	20 ± 3	47 ± 23*	2.774 (0.018)	18 ± 7	41 ± 15*	3.413 (0.006)
Set 2 Reps (#)	13 ± 4	5 ± 4*	-3.219 (0.008)	12 ± 6	4 ± 3*	-3.045 (0.011)
Set 3 Reps (#)	11 ± 5	2 ± 1*	-4.303 (0.001)	9 ± 5	3 ± 3*	-2.872 (0.015)
Total Work (kg · reps)	1590 ± 674	664 ± 418*	-2.950 (0.013)	1530 ± 745	542 ± 244*	-3.323 (0.007)
Exercise Time (min)[†]	1.8 ± 0.5	2.2 ± 0.7	1.194 (0.258)	2.0 ± 0.4	2.3 ± 0.9	1.132 (0.282)
Set 1 time (min)[†]	0.9 ± 0.1	2.0 ± 0.9*	2.997 (0.012)	0.8 ± 0.3	1.8 ± 0.6*	3.424 (0.006)
Set 2 time (min)[†]	0.6 ± 0.1	0.3 ± 0.2*	-2.802 (0.017)	0.5 ± 0.2	0.3 ± 0.1*	-3.250 (0.008)
Set 3 time (min)[†]	0.5 ± 0.2	0.2 ± 0.2*	-3.734 (0.003)	0.5 ± 0.2	0.1 ± 0.1*	-4.172 (0.002)
Heel Raise						
Load (kg)	74.6 ± 31.3	16.6 ± 3.4*	-4.907(< 0.001)	75.2 ± 27.4	16.4 ± 3.3*	-5.672 (< 0.001)
Total Reps (#)	41 ± 12	66 ± 22*	2.469 (0.031)	41 ± 12	67 ± 22*	2.578 (0.026)
Set 1 Reps (#)	17 ± 4	50 ± 21*	3.809 (0.003)	16 ± 4	51 ± 21*	3.880 (0.003)
Set 2 Reps (#)	13 ± 4	11 ± 4	-0.871(0.403)	13 ± 5	10 ± 4	-1.061 (0.311)
Set 3 Reps (#)	11 ± 4	6 ± 5*	-2.413 (0.034)	11 ± 4	6 ± 4*	-2.370 (0.037)
Total Work (kg · reps)	2963 ± 918	1117 ± 464 *	-4.218 (0.001)	2976 ± 918	1117 ± 459*	-3932 (0.002)
Exercise Time (min)[†]	1.1 ± 0.2	1.6 ± 0.3*	2.527 (0.028)	1.16 ± 0.2	1.65 ± 0.4*	2.487 (0.030)
Set 1 time (min)[†]	0.4 ± 0.1	1.1 ± 0.3*	4.985 (< 0.001)	0.45 ± 0.1	1.12 ± 0.3*	5.226 (< 0.001)
Set 2 time (min)[†]	0.4 ± 0.1	0.3 ± 0.1	-0.591 (0.566)	0.37 ± 0.1	0.31 ± 0.1	-1.605 (0.137)
Set 3 time (min)[†]	0.3 ± 0.1	0.2 ± 0.1*	-2.447 (0.032)	0.36 ± 0.1	0.18 ± 0.1*	-3.646 (0.004)

Data are mean ± SD. HL $N = 6$; BFR $N = 7$. Degrees of freedom for all paired *t*-tests were HL = 5, BFR = 6.

* Significantly different from HL within loading condition, $P < 0.05$.

[†] Contraction time only.

Reps = repetitions performed, HL = high-load resistance exercise; BFR = blood flow restricted exercise.

lifted for one repetition through the full range of motion) was determined.

A quantitative assessment of muscle activation was determined using a knee extension device (NT-1220, Nautilus, Inc., Vancouver, WA) by evaluating central activation capacity via interpolated twitch.[2] A constant-current stimulator (Digitimer DS7AH, Welwyn Garden City, UK) was used to deliver a doublet pulse sequence (100 Hz, 200 μs pulse width) to the knee extensors through surface electrodes (7.5 cm × 13 cm self-adhesive carbon-impregnated electrodes; ValuTrode, Axelgaard, Fallbrook, CA) placed on the proximal vastus lateralis and distal vastus medialis. First, the optimal current for eliciting a supramaximal twitch was determined. Doublet pulses were delivered every 20 s in 40-mA increments until twitch torque failed to increase in response to consecutive stimuli or increasing current. Second, an interpolated twitch test was conducted. Subjects were instructed to produce a maximal voluntary contraction (MVC) as quickly as possible and to hold the contraction. At 2.5 s into the MVC, a supramaximal doublet was delivered to the knee extensors to elicit an interpolated twitch. After the twitch subjects were instructed to relax and 2 s later another supramaximal doublet was applied to elicit a potentiated twitch. Force data was sampled at 5000 Hz and low-pass filtered at 220 Hz. One female subject in BFR was unable to complete testing; therefore, central activation capacity data for BFR was analyzed with $N = 6$. Central activation capacity was calculated as: [1 − (interpolated twitch force/potentiated twitch force)] x 100.[25]

An assessment of fine motor control was determined by examining force steadiness of the knee extensors. Using the knee extensor device, a target force of 5% of MVC (measured during the central activation capacity test) was displayed on a 48-cm computer monitor placed 1.5 m from the subject's eyes. Subjects attempted to match the target force output as closely as possible. Each force steadiness test lasted 30 s. Visual feedback was provided during the first 15 s and was removed during the last 15 s, requiring subjects to rely on perception of effort alone. Force data was sampled at 300 Hz and low-pass filtered at 4 Hz. Force steadiness was calculated during the middle 10-s portion of the period when visual feedback was given and during the middle 10-s portion of the period when no visual feedback was given. Force steadiness was expressed as a coefficient of variation (CV), which was calculated as: CV = (SD in force output / mean force output) ^{x} 100. Participants performed three trials, with 30 s rest between efforts. The reliability of central activation capacity and force steadiness testing has been described previously.[25]

To assess single leg muscular endurance of the knee extensors and plantar flexors, repeated dynamic contractions at 40% 1 RM (obtained during the control period) were performed on the Agaton Fitness System. The same absolute workload was used pre- and post-ULLS. The test was terminated when a subject could no longer perform a repetition through the full range of motion. The total number of repetitions was recorded and used for analysis.

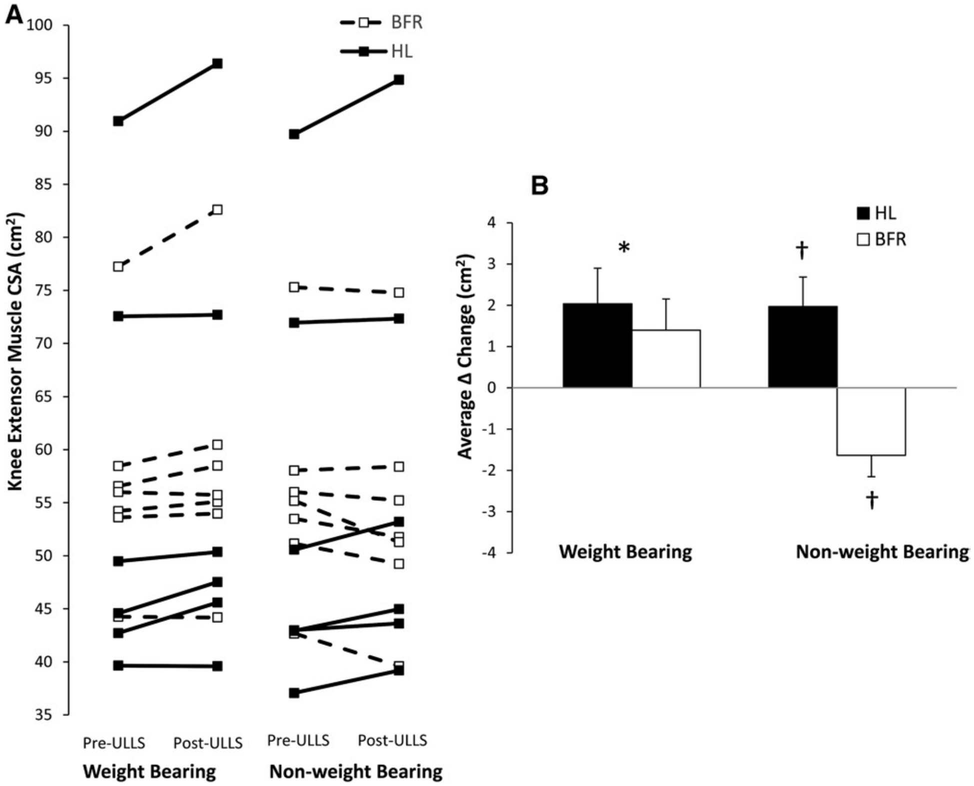

Fig. 1. A) Individual and B) average delta changes in knee extensor CSA in both HL and BFR with or without daily weight bearing. †Condition by time interactions ($P = 0.002$) indicating a significant change from pre-ULLS within the designated loading condition. *Main effect of time ($P = 0.012$) indicating in a significant change from pre-ULLS when both loading conditions were averaged. CSA = cross-sectional area, ULLS = unilateral lower limb suspension, HL = high-load resistance exercise, BFR = blood flow restricted exercise. Data are mean ± SE.

Statistical Analysis

Student *t*-tests were used to evaluate differences in participant descriptive characteristics, ULLS compliance (skin temperature, steps detected), and data associated with the exercise prescription (training load, repetitions performed, total work, and exercise duration). Data in these sections are displayed as mean ± SD. To investigate the effect of exercise condition across time separate repeated measures ANOVAs (within-subjects factor was time, between subjects factor was exercise condition) were performed. The alpha level for all statistical procedures was set at $P < 0.05$. Interactions and effect of weight bearing compared to nonweight bearing were explored by a priori planned comparisons using paired *t*-tests.

RESULTS

All subjects ($N = 13$) completed 25 d of ULLS without any adverse responses to the unloading protocol. Plantar accelerometery showed a significant (99.0%) reduction in the number of steps detected per day of ULLS in the left leg compared to the number detected during the pre-ULLS ambulatory period [1962.96 ± 746.59 vs. 18.77 ± 30.15, $t(12) = 9.513$, $P < 0.001$]. Resting skin temperatures of the nonweight-bearing limbs were significantly lower during ULLS compared to the Pre-ULLS ambulatory period [knee extensors: 27.66 ± 1.11 vs. 27.07 ± 0.92°C, $t(12) = 2.355$, $P = 0.036$; plantar flexors: 28.559 ± 0.8 vs. 27.28 ± 0.80°C, $t(12) = 5.586$, $P < 0.001$]. Total energy intake during ULLS was not different [$t(11) = -4.30$, $P = 0.676$] between HL (111.87 ± 32.95 kJ $\cdot$ kg^{-1} $\cdot$ d^{-1}) and BFR (104.89 ± 25.69 kJ $\cdot$ kg^{-1} $\cdot$ d^{-1}). Macronutrient composition was also not different between HL and BFR, respectively, for fat [0.95 ± 0.34 vs. 0.96 ± 0.40 g $\cdot$ d^{-1} $\cdot$ kg^{-1}, $t(11) = 0.098$, $P = 0.924$], protein [1.12 ± 0.23 vs. 1.19 ± 0.29 g $\cdot$ d^{-1} $\cdot$ kg^{-1}, $t(11) = 5.15$, $P = 0.24$], or carbohydrates [3.46 ± 1.06 vs. 3.46 ± 1.28 g $\cdot$ d^{-1} $\cdot$ kg^{-1}, $t(11) = 0.007$, $P = 0.995$]. Post-ULLS, body mass did not significantly deviate from pre-ULLS [68.34 ± 12.96 to 68.74 ± 13.34 kg, $t(12) = -1.181$, $P = 0.260$]. Participants exercised both nonweight-bearing and weight-bearing limbs 3 d/wk during ULLS (9 ± 1 exercise sessions per subject). Leg press and heel raise training load, repetitions performed, total work, and exercise duration are shown in **Table I**.

There was an exercise condition by time interaction [$F(1,11)=16.161$, $P = 0.002$] for knee extensor muscle CSA in the nonweight-bearing limb, where HL increased (54.8 ± 8.3 to 56.8 ± 8.6 cm^2) and BFR decreased (54.9 ± 3.7 to 53.3 ± 4.0 cm^2) post-ULLS. In contrast, in the weight-bearing limb, knee extensor muscle CSA increased [main effect, $F(1,11) = 8.956$, $P = 0.012$] from pre- to post-ULLS in both HL (56.6 ± 8.4 to 58.6 ± 8.8 cm^2) and BFR (57.3 ± 3.6 to 58.7 ± 4.4 cm^2, **Fig. 1**). There was also an exercise condition by time interaction [$F(1,11) = 8.256$, $P = 0.015$] for plantar flexor muscle CSA in the nonweight-bearing limb, where muscle CSA in HL was maintained (37.7 ± 4.2 to 38.1 ± 4.1 cm^2), but decreased significantly in BFR (37.5 ± 2.2 to 35.7 ± 2.2 cm^2). In the weight-bearing limb, plantar flexor CSA increased from pre to post-ULLS [main effect, $F(1,11) = 10.176$, $P = 0.009$] in both HL (37.3 ± 4.7 to 39.1 ± 5.1 cm^2) and BFR (38.1 ± 2.0 to 39.4 ± 2.5 cm^2, **Fig. 2**).

There was a significant exercise condition by time interaction for leg press 1 RM in the nonweight-bearing limb [$F(1,11) = 9.581$, $P = 0.010$], where strength was maintained in HL (59.3 ± 12.1 to 64.6 ± 12.6 kg), but decreased significantly in BFR (49.9 ± 6.1 to 43.9 ± 5.6 kg). There was also a significant exercise condition by time interaction for leg press 1 RM in the weight-bearing limb [$F(1,11) = 9.106$, $P = 0.012$], where the increase in strength post-ULLS in HL (52.9 ± 11.0 to 64.6 ± 12.6 kg) was to a greater extent than that of BFR (51.0 ± 7.2 to 53.6 ± 6.7 kg, **Fig. 3**). For plantar flexion 1 RM, there was a significant exercise condition by time interaction in the nonweight-bearing limb [$F(1,11) = 5.908$, $P = 0.033$], where strength increased in HL (94.5 ± 14.0 to 103 ± 16.3 kg) post-ULLS and was maintained in BFR (84.9 ± 6.6 to 74.8 ± 3.1 kg). In contrast, plantar flexion 1 RM in the weight-bearing limb increased post-ULLS [main effect, $F(1,11) = 14.122$, $P = 0.003$] in HL (93.8 ± 15.6 to 108.1 ± 115.6 kg) and BFR (86.8 ± 7.6 to 92.3 kg, **Fig. 4**). The differences when comparing muscle CSA and strength adaptations in the nonweight-bearing relative to the weight-bearing limbs are shown in **Table II**. There were no significant main effects or interaction effects for central activation capacity or force steadiness in nonweight-bearing or weight-bearing limbs in either HL or BFR (**Table III**).

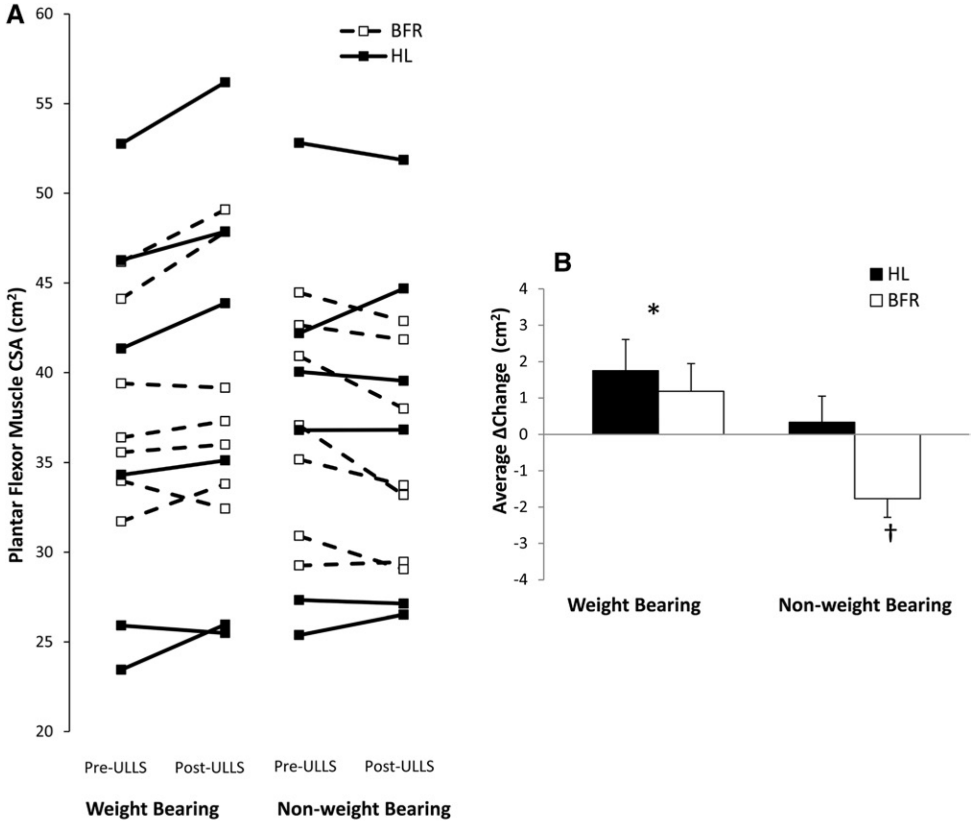

Fig. 2. A) Individual and B) average delta changes in plantar flexor CSA in both HL and BFR with or without daily weight bearing. †Condition by time interactions ($P = 0.015$) indicating a significant change from pre-ULLS within the designated condition. *Main effect of time ($P = 0.009$) indicating in a significant change from pre-ULLS when both conditions were averaged. CSA = cross-sectional area, ULLS = unilateral lower limb suspension, HL = high-load resistance exercise, BFR = blood flow restricted exercise. Data are mean ± SE.

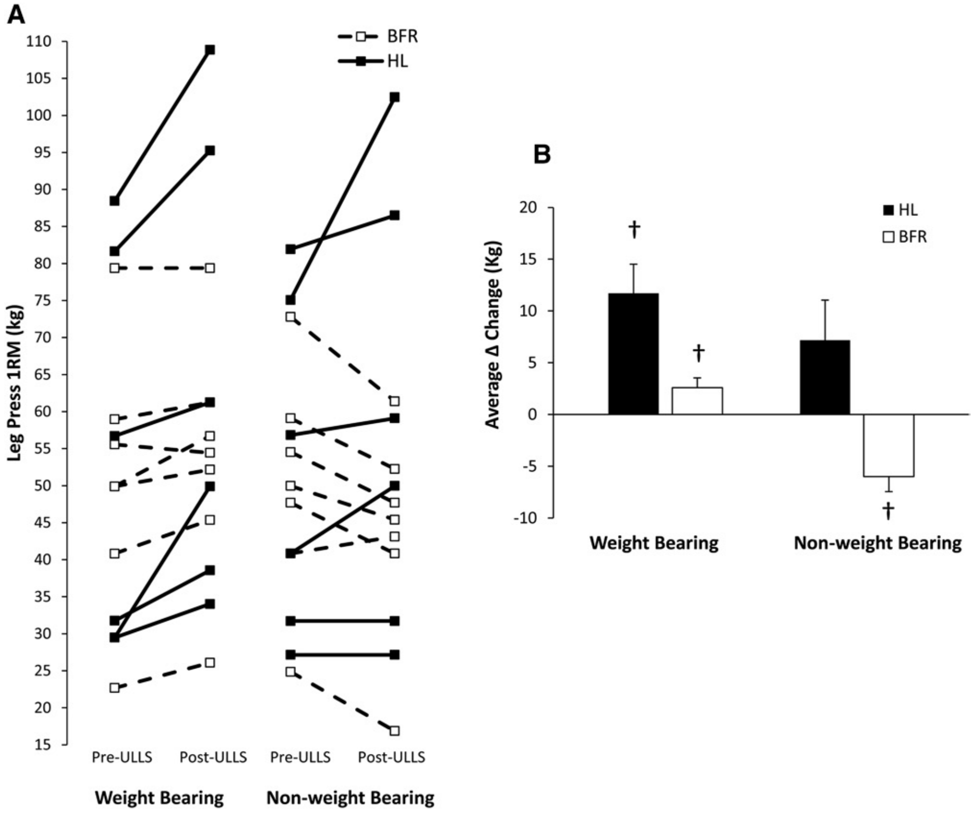

Fig. 3. A) Individual and B) average delta changes in leg press 1 RM in both HL and BFR with or without daily weight bearing. †Condition by time interactions (nonweight-bearing, $P = 0.010$; weight-bearing, $P = 0.012$) indicating a significant change from pre-ULLS within the designated condition. 1 RM = one repetition maximum, ULLS = unilateral lower limb suspension. HL = high-load resistance exercise; BFR = blood flow restricted exercise. Data are mean ± SE.

Dynamic leg press endurance in the nonweight-bearing limb did not change pre- to post-ULLS in HL or BFR [interaction, $F(1,11) = 0.268$, $P = 0.615$]. In the weight-bearing limb, leg press endurance increased from pre- to post-ULLS [main effect, $F(1,11) = 5.856$, $P = 0.034$] in both HL and BFR. There was a trend toward an interaction effect for plantar flexor dynamic endurance in both the nonweight-bearing [interaction, $F(1,11) = 4.572$, $P = 0.056$] and weight-bearing legs [interaction, $F(1,11) = 3.631$, $P = 0.083$]. Additionally, there were significant main effects from pre- to post-ULLS in the nonweight-bearing [main effect, $F(1,11) = 18.996$, $P = 0.001$] and weight-bearing [main effect, $F(1,11) = 16.479$, $P = 0.002$] limbs for both HL and BFR (**Table IV**).

DISCUSSION

The main finding of this investigation was that HL resistance exercise training facilitated increases in muscle CSA and strength in both nonweight-bearing and weight-bearing limbs, whereas BFR training did not prevent muscle atrophy or strength decrements in the unloaded limb. These data indicate that HL resistance training should be prescribed to astronauts during long duration spaceflight in order to most effectively and efficiently maintain muscle size and strength. BFR exercise could be a viable option in at least mitigating muscle atrophy when HL training equipment is not available or if there is an injury that could prevent HL training from occurring.[22]

In the absence of any countermeasures, previous work has shown knee extensor and plantar flexor muscle CSA in the unloaded limb declines by 7–9% over a ~25-30-d period.[8] The finding that HL resistance exercise training during 25 d of unloading resulted in muscle hypertrophy in the knee extensors (+3.6%) and a maintenance (+1.1%) of muscle size in the plantar flexors was unexpected. Many studies show a preservation of muscle CSA or strength;[17] however, the stimulation of muscle growth during a 25-d unloading period is rare. Tesch et al. (using a flywheel exercise device) is the only other study to elicit significant muscle growth (+8.8%) in the knee extensors during an equivalent duration of limb unloading.[28] Although the BFR exercise training was not able to fully preserve muscle CSA during ULLS, it should be noted that compared to another ULLS study of a similar duration without exercise training,[8] our BFR exercise training mitigated muscle atrophy by approximately 50%. However, our data suggest HL resistance exercise is more effective than BFR exercise as a countermeasure to prevent unloading induced muscle atrophy.

By simultaneously evaluating the exercise adaptations in weight-bearing limbs and nonweight-bearing limbs we are able to better understand the effects of the specific training modality as well as the effects of training and unloading within the same subject. Previous work has shown that ULLS alone (up to 6 wk) does not change the CSA of the knee extensor muscles in the weight-bearing leg, suggesting an additional stimulus is required to initiate muscle growth.[13] Both HL and BFR exercise induced increases in knee muscle CSA when combined with the weight-bearing limb and the changes were relatively similar for both the knee extensors (2–4%) and plantar flexors (3–5%). These data are consistent with training studies showing blood flow restricted exercise is an effective alternative to HL resistance exercise to stimulate muscle growth in ambulatory populations.[26,27] However, when comparing differences in the nonweight-bearing limb to the weight-bearing limb with each exercise training modality (Table II), there were striking differences in efficacy. HL exercise in the nonweight-bearing leg did not show any significant decrement in effectiveness (e.g., CSA, 1 RM) when compared to the weight-bearing leg. In contrast,

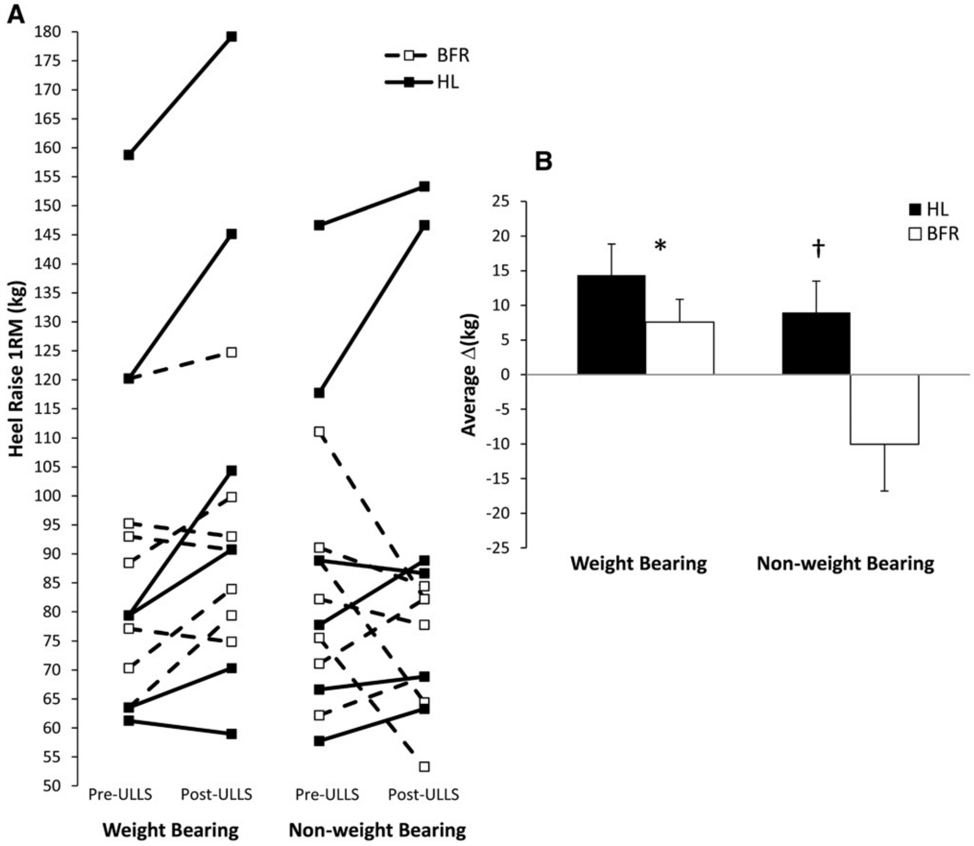

Fig. 4. A) Individual and B) average delta changes in heel raise 1 RM in both HL and BFR with or without daily weight bearing. †Condition by time interactions (*P* = 0.033) indicating a significant change from pre-ULLS within the designated condition. *Main effect of time (*P* = 0.003) indicating in a significant change from pre-ULLS when both conditions were averaged. 1 RM = one repetition maximum, ULLS = unilateral lower limb suspension. HL = high-load resistance exercise; BFR = blood flow restricted exercise. Data are mean ± SE.

BFR exercise in the nonweight-bearing leg showed significant adaptive declines ranging from 5–18% when compared with the weight-bearing limb. These data reinforce that BFR exercise should be considered an adjunct countermeasure rather than a primary exercise method to preserve muscle CSA and strength.

Any loss of muscle strength following unloading via ULLS with or without countermeasures cannot be fully explained by the observed decrease in muscle CSA alone, indicating that unloading also results in reduced neuromuscular activation and/or coordination.[6] In our investigation, BFR exercise training in the nonweight-bearing limb attenuated strength loss, but still resulted in 12.8% and 9.9% reductions in both knee extensor and plantar flexor 1 RM, respectively. In contrast, HL resistance exercise not only stimulated hypertrophy in the nonweight-bearing limb, it also fostered 11% and 10% increases in knee extensor and plantar flexor 1 RM. Hence, HL resistance training fully preserved muscle strength in the lower limb during prolonged unloading, while BFR exercise only attenuated the strength loss. Our data do allow for determination of the effectiveness of HL or BFR exercise toward protecting neuromuscular activation given there were no significant changes in central activation capacity, nor was there a significant association with the change in strength (R = 0.11). In the absence of alterations in muscle activation, it is plausible that changes in tendon elasticity could have influenced the strength adaptations as previously shown following 23 d of ULLS.[10] Alternatively, the pattern of strength adaptation was slightly different in the weight-bearing limb. Consistent with previous literature,[5] high-load training resulted in increased leg press (+25.6%) and plantar flexor strength (+14.4%), which was not significantly greater than the 6.6% and 7.6% gains observed with blood flow restricted exercise training. Why blood flow restricted exercise training would be efficacious when used with daily weight bearing, but less successful during unloading has yet to be determined.

Table II. Adaptations Relative to Weight-Bearing Leg.

ADAPTATION	DIFFERENCE (%)	*t*-SCORE	*P*-VALUE
HL			
Knee extensor CSA	+0.31	0.175	0.867
Leg press 1RM	−8.37	−1.732	0.144
Plantar flexor CSA	−3.79	−1.463	0.203
Plantar flexor 1RM	−5.92	−1.371	0.229
BFR			
Knee extensor CSA	−5.52	−5.942	0.001*
Leg press 1RM	−17.09	−6.574	0.001*
Plantar flexor CSA	−7.82	−4.898	0.003*
Plantar flexor 1RM	−18.18	−3.667	0.010*

Data are percent difference in the nonweight-bearing leg relative to the weight-bearing leg. HL = high-load resistance exercise; BFR = blood flow restricted exercise; CSA = cross-sectional area. Degrees of freedom for all paired *t*-tests were HL = 5, BFR = 6.

Most resistance training studies focus on the effectiveness of the countermeasure toward the maintenance of muscle strength; however, muscle endurance is also a very important parameter to include in the assessment of a countermeasure's effectiveness for astronauts because they are rarely asked to perform maximal activities. Rather, emergency egress, extravehicular activity, and future exploration activities typically require repetitive submaximal levels of effort. Cook et al. previously showed knee extensor muscular endurance was reduced 24.0% following unloading via ULLS in the absence of any exercise countermeasures and BFR exercise training over that period stimulated a 28% improvement in muscular endurance.[8] This endurance adaptation suggests a metabolic profile that is optimized to resist fatigue. In the unloaded limb, BFR exercise resulted in highly variable leg press endurance adaptations

Table III. Central Activation Capacity and Force Steadiness.

	WEIGHT-BEARING				NONWEIGHT-BEARING			
	HL		BFR		HL		BFR	
	PRE-ULLS	POST-ULLS	PRE-ULLS	POST-ULLS	PRE-ULLS	POST-ULLS	PRE-ULLS	POST-ULLS
CAC (%)	89.8 ± 6.1	84.7 ± 5.0	77.3 ± 10	78.9 ± 14.9	85.2 ± 3.23	91.8 ± 5.9	77.4 ± 9.6	77.2 ± 10.5
StdV (CV%)	2.1 ± 0.7	2.4 ± 1.1	2.0 ± 0.8	2.0 ± 0.7	2.4 ± 1.0	2.7 ± 1.7	2.3 ± 1.0	3.1 ± 2.2
StdNV (CV%)	2.5 ± 0.6	2.7 ± 1.1	1.9 ± 0.7	1.9 ± 0.6	2.6 ± 1.2	2.9 ± 1.4	1.8 ± 0.6	2.0 ± 0.5

Data are mean ± SD. No significant changes for any variable ($P > 0.05$). HL $N = 6$; BFR $N = 6$; CAC = central activation capacity, StdV = visual feedback provided with force steadiness test, StdNV = no visual feedback provided with force steadiness test, CV = coefficient of variation, HL = high-load resistance exercise; BFR = blood flow restricted exercise; ULLS = unilateral lower limb suspension.

ranging from 5 to 88% (average 22.5%) increases, while HL resistance exercise showed a decrement in muscular endurance by 6.8%. In the unloaded plantar flexors, however, the change in muscular endurance approached significance, whereby muscular endurance improved 48.2% with blood flow restricted exercise training and 17.5% with high load training.

In the weight-bearing limb, leg press muscle endurance increased similarly in both exercise conditions (39.2% and 31.6% in HL and BFR, respectively). In the plantar flexors the change in muscular endurance approached significance, in which BFR increased 40.9% compared to the 17.7% increase with HL exercise. Overall, these data provide evidence to suggest blood flow restricted exercise may be a greater stimulus to elicit adaptations to resist fatigue, but the response is highly variable. Increased basal muscle glycogen content may be one of the mechanisms that could explain any improvements in muscular endurance with blood flow restricted exercise training, as it has been shown to elevate as an adaptation following this type of training.[4] The observed high level of individual variability requires further investigation in order to provide exercise prescriptions that will elicit improvements in muscle endurance.[8] Currently, there is no agreement among scientists on how cuff pressure should be prescribed given other programming variables such as cuff width, cuff placement, blood pressure, and age.[24] Some studies also use a fixed 4-set, 30-, 15-, 15-, 15-repetition protocol,[15] while others, including this study, performed repetitions to fatigue.[8] Further, there was less total work (kg · repetitions) performed in BFR with very few repetitions completed in sets 2 and 3 in BFR relative to HL. Surely, these factors could influence exercise training adaptations and explain some of the observed variability. A potential way to increase the total work in BFR would be to deflate the cuff during the rest intervals; however, the same metabolic stress and anabolic response (e.g., growth hormone) may not be achieved.[21] Attempting to match the total work performed in BFR to HL could warrant future research, especially in a spaceflight analogue such as ULLS or bed rest.

In conclusion, HL resistance exercise and BFR resistance exercise were evaluated in weight-bearing and nonweight-bearing legs before and after 25 d of ULLS. HL resistance promoted muscle hypertrophy and strength gains in both weight-bearing and nonweight-bearing limbs. In contrast, the exercise training adaptations to BFR exercise were dampened in the unloaded leg compared to the weight-bearing leg. Based on our results, HL resistance exercise is the most viable option to preserve muscle CSA and strength, while BFR exercise may be used as an adjunct countermeasure, particularly in the area of fatigue resistance. The type of work required during the long duration spaceflight mission, the main goal of the exercise countermeasure, and the specific exercise hardware available should be considered prior to prescribing exercise protocols to astronauts or individuals during bed rest or other unloaded conditions.

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Table IV. Dynamic Endurance Adaptations (Repetitions at 40% of Pre-ULLS 1 RM).

	WEIGHT-BEARING				NONWEIGHT-BEARING			
	HL		BFR		HL		BFR	
	PRE-ULLS	POST-ULLS	PRE-ULLS	POST-ULLS	PRE-ULLS	POST-ULLS	PRE-ULLS	POST-ULLS
Leg Press	40.8 ± 18.9	46.2 ± 7.1*	36.6 ± 11.9	47.1 ± 13.1*	45.0 ± 17.1	39 ± 12.5	35.1 ± 8.3	41.71 ± 7.2
Heel Raise	33.0 ± 12.3	37.3 ± 10.9*	28.9 ± 8.3	40.9 ± 14.3*	32.2 ± 10.2	37.1 ± 9.6*	29.4 ± 8.4	43.7 ± 15.3*

Data are mean ± SD. *Main effect; significant increase pre- to post-ULLS for average of HL and BFR, $P < 0.05$. HL = high-load resistance exercise; BFR = blood flow restricted exercise, ULLS = unilateral lower limb suspension.

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