Mobile Lower Body Negative Pressure Suit as an Integrative Countermeasure for Spaceflight

Lonnie G. Petersen; Alan Hargens; Elizabeth M. Bird; Neeki Ashari; Jordan Saalfeld; Johan C. G. Petersen

BACKGROUND: Persistent headward fluid shift and mechanical unloading cause neuro-ocular, cardiovascular, and musculoskeletal deconditioning during long-term spaceflight. Lower body negative pressure (LBNP) reintroduces footward fluid shift and mechanical loading.

METHODS: We designed, built, and tested a wearable, mobile, and flexible LBNP device (GravitySuit) consisting of pressurized trousers with built-in shoes to support ground reaction forces (GRF) and a thoracic vest to distribute load to the entire axial length of the body. In eight healthy subjects we recorded GRF under the feet and over the shoulders (Tekscan) while assessing cardiovascular response (Nexfin) and footward fluid shift from internal jugular venous cross-sectional area (IJVa) using ultrasound (Terason).

RESULTS: Relative to normal bodyweight (BW) when standing upright, increments of 10 mmHg LBNP from 0 to 40 mmHg while supine induced axial loading corresponding to 0%, 13 ± 3%, 41 ± 5%, 75 ± 11%, and 125 ± 22% BW, respectively. Furthermore, LBNP reduced IJVa from 1.12 ± 0.3 cm^2 to 0.67 ± 0.2, 0.50 ± 0.1, 0.35 ± 0.1, and 0.31 ± 0.1 cm^2, respectively. LBNP of 30 and 40 mmHg reduced cardiac stroke volume and increased heart rate while cardiac output and mean arterial pressure were unaffected. During 2 h of supine rest at 20 mmHg LBNP, temperature and humidity inside the suit were unchanged (23 ± 1°C; 47 ± 3%, respectively).

DISCUSSION: The flexible GravitySuit at 20 mmHg LBNP comfortably induced mechanical loading and desired fluid displacement while maintaining the mobility of hips and knee joints. The GravitySuit may provide a feasible method to apply low-level, long-term LBNP without interfering with daily activity during spaceflight to provide an integrative countermeasure.

KEYWORDS: integrative countermeasure, spaceflight associated neuro-ocular syndrome, mechanical loading.

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Because most parts of the human body and physiology are affected by long-term spaceflight, an integrative countermeasure approach is warranted. Entry into weightlessness causes immediate and sustained fluid shift toward the head which, compared to upright postures on Earth, increases central and cranial blood and fluid filling.[4,29,31] Due to the lack of gravitational stress, astronauts are not able to "stand up" and periodically unload cerebral structures, leading to a situation of mild but chronic cephalad fluid congestion, which we[22,32,35] and others[37] have hypothesized to be an initiating and driving factor in development of Spaceflight Associated Neuo-ocular Syndrome (SANS).[23,27] Additionally, mechanical unloading and reduced overall physical activity associated with weightlessness negatively impacts the cardiovascular system, reduces oxidative capacity, and causes atrophy of the musculoskeletal system.[8,10,28] We have recently documented the efficacy of low-level lower body negative pressure (LBNP) to unload cephalad fluid congestion and reduce intracranial pressure.[32] Moreover, LBNP can be used to generate mechanical loading of the body[14,15,20] and exercise within LBNP is efficient in maintaining oxidative capacity and counteracting muscle loss during

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bedrest.[30] A compelling approach to an integrative countermeasure for long-term spaceflight is, therefore, application of LBNP to generate both gravitational fluid shifts and mechanical forces on the body.[16,20,39] To increase feasibility of LBNP for spaceflight, we designed, built, and tested a wearable and mobile LBNP device (GravitySuit) which could possibly be worn for hours without interfering with daily activity. Furthermore, if the wearable LBNP device is flexible and allows for mobility of the hip and knee joints, it may be combined with some forms of both dynamic and restrictive exercise. We tested the hypothesis that application of incremental LBNP by the GravitySuit during simulated weightlessness would simulate effects of gravitational stress by inducing mechanical loading of the body, with caudal displacement assessed from decreases in internal jugular venous cross-sectional area (IJVa).

METHODS

Subjects

The protocol was reviewed and approved by the Institutional Review Board at the University of California, San Diego. All participants were informed of the purpose and risks involved with each procedure and provided oral and written informed consent in compliance with the Declaration of Helsinki. Eight healthy subjects were included [six women; average ± SD (range): age 24 ± 6 yr (18–39); height 168 ± 6 cm (165–178); weight 57 ± 8 kg (48–70)]. All had abstained from caffeine, alcohol, and strenuous exercise for at least 12 h prior to testing, none had cardiovascular or musculoskeletal disease, or took any prescription or over-the-counter medication at the time of the investigation.

Equipment and Materials

We designed and built a wearable LBNP device consisting of a set of trousers with an attached vest. The outer shell consists of airtight fabric suspended by a noncollapsible structural framework. The framework is comprised of two flexible cylinders, each containing seven individual polyethylene rings around each leg connected to a double waist ring (**Fig. 1A**). As each individual ring is mobile relative to the next, flexibility and maneuverability is maintained (**Fig. 1B**), allowing for ambulation and some forms of exercise while wearing the suit with LBNP applied. A seal is created at the iliac crest by a flexible neoprene and nylon skirt attached to the top part of the trousers. The fabric forms a continuous shell from the waist seal and encompasses shoes at the end of each leg of the trousers which thereby provide a solid base to allow for generation of ground reaction forces (GRF) under the sole of each foot. To achieve full axial compression of the body and spine as well as to increase comfort during use, a vest was attached to the waist section by three adjustable buckles (two in front and one in the back). Negative pressure is generated by a portable vacuum contained in a flame-resistant pouch attached to the waist area which is run off a rechargeable battery likewise contained in a flame-resistant pouch at the waist. Pressure is regulated by a stepless dial and the pressure difference between the inside and the outside of the device is recorded by built-in sensors (internal sensor and external sensor) and displayed on an LCD screen attached to the waist. Two safety check-release valves are attached at each leg and are triggered at the preset level of negative pressure. When this value is reached, the valves open and create a "controlled leak" and the resultant influx of air maintains the level of LBNP inside the device.

Mechanical loading was quantified as GRF under the sole of each foot using force sensor insoles (Tekscan, South Boston, MA, USA) placed inside the built-in shoe of the GravitySuit as well as mechanical pressure on the shoulders under the vest. Mechanical pressures were recorded continuously and represented as the average of 1 min following 5 min of rest at each pressure level.

Caudal fluid shift was assessed from the reductions in IJVa using ultrasound (Terason t3200, Terason, Burlington, MA, USA). The right IJV was imaged at the level of the cricoid cartilage and care was taken to ensure no change of angle of insonation between LBNP levels. Five images were recorded and values averaged for baseline and at each level of LBNP, ensuring even distribution across cardiac and respiratory cycles.

Continuous arterial blood pressure and heart rate were recorded using the volume-clamp method from a cuff around the third finger and adjusted to heart-level by a height-sensor fixed at the 4^{th} intercostal space. Pulse contour analysis provided cardiac stroke volume, cardiac output, and total peripheral resistance (Nexfin, BMeye, Amsterdam, The Netherlands). Values were recorded continuously and presented as the average of 1 min following 5 min of rest at each condition. Range of motion was recorded as maximum comfortable angle of flexion of the hip and knees from the normal position.

Procedure

Subjects remained in a supine position for the duration of the experiment. To avoid friction forces between the subject and the surface due to the front-to-back gravitational load (1 G_x) and to allow for movement in all three dimensions similar to a weightless environment, we used a suspension system in which the subject's head, neck, and thorax were supported by a backboard while the pelvic area and legs were supported by five individual pulleys.[7] Incremental LBNP from 0 to 40 mmHg at increments of 10 mmHg were applied while subjects were resting in the suspended supine position. Following completion of the incremental protocol, LBNP was set at 20 mmHg and range of motion at this level was recorded.

Statistical Analysis

To determine the effects of LBNP on GRF, reduction in IJVa, and cardiovascular variables, a one-way ANOVA was applied followed by Dunnett's multiple comparisons test. Statistical significance was set at $P < 0.05$. All analysis was performed using GraphPad Prism version 8.1.0 for macOS (GraphPad Software, San Diego, CA, USA). All values are presented as mean ± SD with absolute values provided in the Results section and depicted in figures as normalized values and percent changes compared to baseline supine-suspended posture with no LBNP

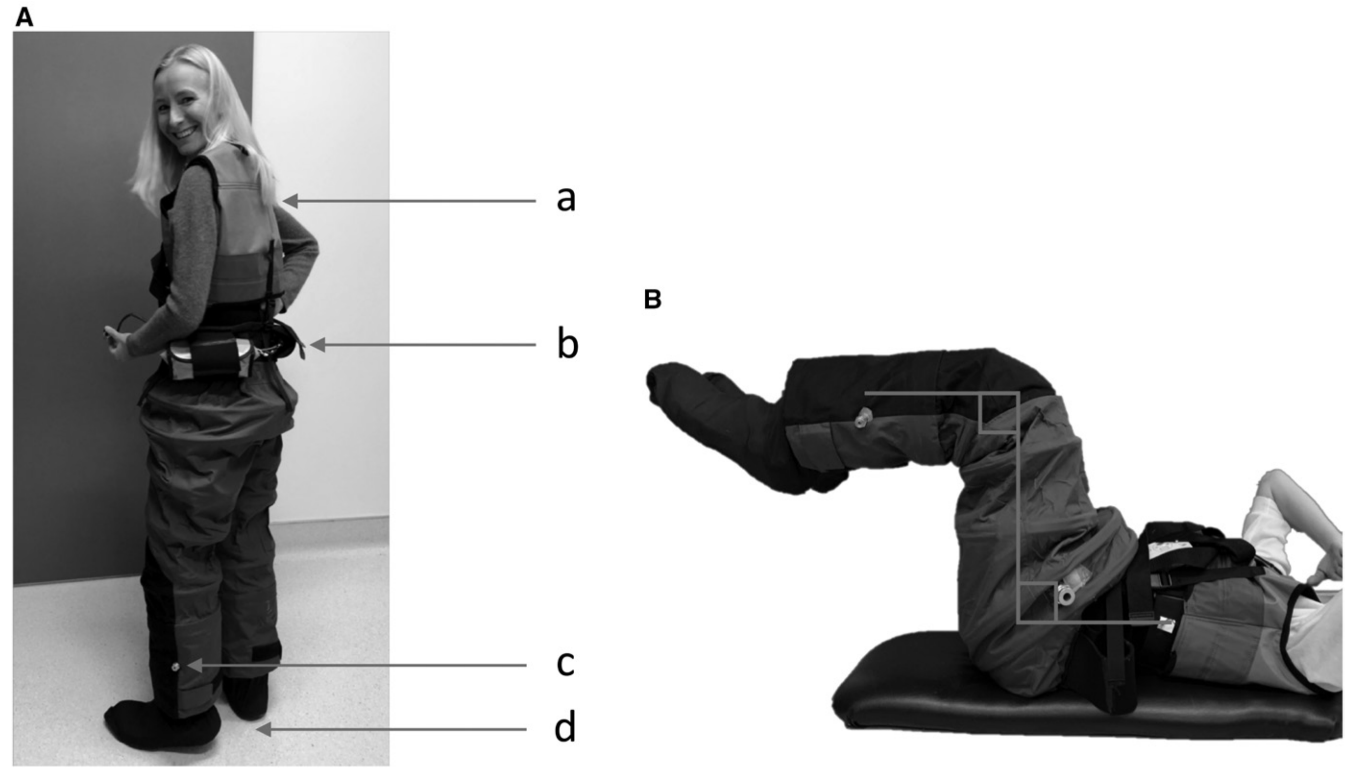

Fig. 1. GravitySuit. A) Photo of GravitySuit and components: a) axial and spinal loading vest; b) utility belt containing vacuum pump, battery pack, pressure sensor, and regulatory unit; c) pressure release check valves; d) built-in shoes to support generation of ground reaction forces. B) Illustration of range of motion; 90° flexion of hip and knee joints. See also film clip: https://youtu.be/3w1GPK9DTPI.

applied. Nonlinear regression and best-fit analysis using the second order polynomial equation was applied to determine the relationship between LBNP level and resulting GRF.

RESULTS

Relative to normal bodyweight (BW) when standing upright, increments of 10 mmHg LBNP from 0 to 40 mmHg while resting in the suspended-supine position generated axial loading corresponding to 0%, 13 ± 3%, 41 ± 5%, 75 ± 11%, and 125 ± 22% BW ($N = 6$; $P < 0.05$; **Fig. 2**). Nonlinear regression best-fit analysis yielded the following equation for the generated GRF:

$$\%BW = 0.06 * LBNP^2 + 0.81 * LBNP + 0.15 \text{ (amalgamated } R^2 = 0.76, P < 0.05).$$

From this, 35.3 mmHg LBNP is the average level that generated 1 BW, while an average 30-mmHg LBNP generated BW was 74.5 ± 25.6%, and at 40 mmHg LBNP BW reached 124.4 ± 54.6%, demonstrating a relatively large variability in GRF. In two subjects, compression forces between the vest and the shoulder were recorded and combined for the two shoulders and found to increase from a total of 0 kg to 2.2 ± 0.1 kg, 3.8 ± 2.0, 5.6 ± 2.1 kg, and 9.5 ± 3.1 kg, respectively (no statistical analysis was applied to this small subgroup; data are presented here merely as proof of concept).

Caudal fluid displacement was indicated by the significant reduction of IVJa from 1.12 ± 0.3 cm^2 (suspended supine value) to 0.67 ± 0.2, 0.50 ± 0.1, 0.35 ± 0.1, and 0.31 ± 0.1 cm^2, respectively ($N = 8$; $P < 0.05$; **Fig. 3**). Cardiovascular parameters were well maintained ($N = 8$; $P > 0.05$), with the exception of stroke volume (SV), which decreased at 40 mmHg and was accompanied by a nonsignificant increase in heart rate (HR). Mean arterial blood pressure (MAP) was maintained throughout the incremental LBNP protocol (**Fig. 4**).

While maintaining LBNP at 20 mmHg and with their weight supported by the pulleys of the suspension system, subjects were able to move comfortably and simulate certain forms of exercise maneuvers compatible with, e.g., rowing, squats, or jogging exercises. Range of motion across the hip and knee joints was measured and confirmed to reach 90° (Fig. 1B). A short film clip is provided (https://youtu.be/3w1GPK9DTPI) demonstrating mobility and flexibility of the suit during application of 20-mmHg LBNP. During 2 h of supine rest at 20 mmHg LBNP for an $N = 1$, temperature and humidity inside the suit were unchanged: 23.2 ± 1°C; 47.6 ± 2.6%, respectively.

DISCUSSION

LBNP is a potential countermeasure to reverse the cranial fluid shift associated with weightlessness.[22,32] Here we demonstrate that a similar fluid shift and unloading of cranial structures, as indicated by a significant reduction in IJVa, can be generated

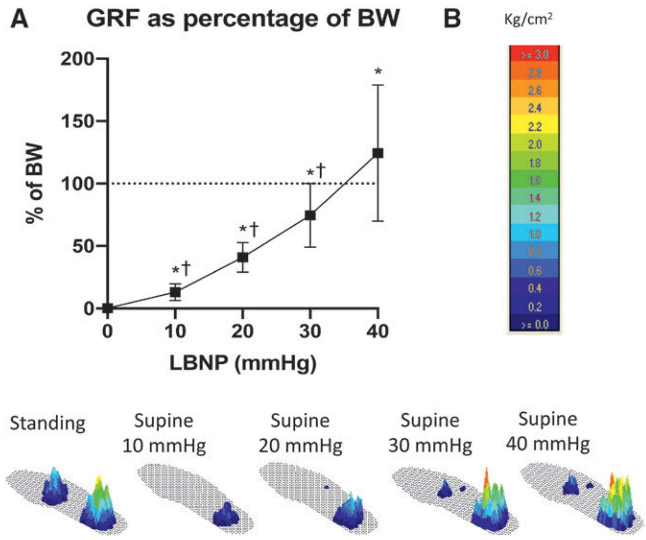

Fig. 2. Ground reaction forces (GRF). A) GRF expressed as percentage of bodyweight (BW) when standing upright as a function of incremental lower body negative pressure (LBNP) from 0 to 40 mmHg ($N = 6$). Values are mean ± SD. *Indicates $P < 0.05$ compared to baseline (0 mmHg of LBNP); †indicates $P < 0.05$ compared to the preceding level of LBNP. B) Example of GRF generated under the right foot as a function of incremental LBNP: "Standing" is included as baseline and demonstrates the pressure generated under the foot by standing up. As the subject is supine no GRF is generated; as LBNP is increased to 10 mmHg, GFR are generated and increases as LBNP is increased.

from a wearable mobile LBNP suit. In addition to displacing blood and fluid caudally, the negative pressure also displaces the body of the subject in the device, thereby generating mechanical forces under the feet. These forces were augmented by axial compression of the flexible device correlating to the level of LBNP applied and distributed to the entire length of the body by the vest. Taken together, the intravehicular GravitySuit may provide a feasible method for simulating beneficial effects of gravitational stress during spaceflight as an integrative countermeasure.

With increasing mission length, more astronauts develop one or more symptoms, including optic disc edema, globe flattening, choroidal and retinal folds, cotton-wool spots, and visual changes collectively referred to as SANS.[23,27] Associated changes in brain structure, the cerebrospinal fluid system, and cognitive function following long-duration spaceflight also raise concern.[11,34,35] Neuro-ocular symptoms carry significant risk both for individual crewmembers and overall mission integrity. While the exact etiology behind SANS remains unknown, multiple mechanisms have been proposed[37] and are likely not mutually exclusive. An early and still relevant theory is that cranial fluid shift associated with weightlessness and chronic cephalad congestion during long-term missions is a key factor.[27] Indeed, SANS and SANS-associated findings are compatible with an intracranial fluid build-up or pressure increase.[22,32,37] Humans are adapted to the constant stress of gravity and usually spend two-thirds of every day in upright postures.[5] When standing, gravity displaces blood and fluid toward the feet, which decreases intracranial pressure (ICP)[2,33] and reduces choroidal volume.[1] These diurnal fluctuations in pressure and volume are lost in space and may be an aggravating stimulus for the remodeling of the eye and brain.[22]

A compelling countermeasure strategy is, therefore, to reintroduce gravitational fluid shift by LBNP to unload cerebral structures,[32] albeit dose (level and time) of LBNP needed to ameliorate SANS remains unknown. During decades of long-term (up to 90 d) bedrest trials, symptoms of SANS have not been prevailing, which may be explained by the fact that these subjects have typically been allowed to elevate their heads for meals and personal hygiene. Head elevation, even if brief, facilitates drainage of cerebral structures and immediate reduction in ICP.[33] Periodic cerebral unloading may, therefore, be sufficient to prevent SANS or keep symptoms to subclinical levels. This is supported by recent data from Laurie and coworkers, who demonstrated early signs of SANS in a ground-based analog by using a "strict" head-down tilt bedrest model, where the head is not elevated above heart level at any point.[21] In recent preclinical trials, we have demonstrated the dose-response relationship between LBNP and reduction in ICP and showed 20–25 mmHg LBNP as a safe and efficient level to reduce ICP.[32] Taken together, periodic application of low-level LBNP could hold potential as a countermeasure for SANS.

LBNP was used in the Apollo program to test for postflight orthostatic intolerance.[15,16] Different configurations of LBNP-devices have been used during spaceflight for decades, including the Skylab program and Mir.[19] Currently the Russian LBNP device ("Chibis") is available onboard the International Space Station.[20] However, alternative mechanical countermeasures have been proposed to reduce cranial fluid and pressure such as venous thigh cuffs, which mechanically hinder venous return from the legs to sequester blood and fluid.[13] Impedance threshold devices provide an inspiratory resistance, thereby reducing intrathoracic pressure and ICP.[9,13]

The cardiovascular system is particularly sensitive to changes in gravitational stress and postflight orthostatic intolerance and reduced oxidative capacity remain a risk despite a rigorous in-flight exercise countermeasure program.[6,8,25] Spaceflight of 6 mo leads to significant thickening and stiffening of carotid and peripheral arteries comparable to aging 10–20 yr,[3,18] as well as increased oxidative stress and indications of elevated risk of cardiovascular disease, correlating to mission length.[11,17] LBNP as a countermeasure was beneficial for maintaining orthostatic tolerance and exercise capacity.[12,24] The GravitySuit presented here provides a feasible method to comfortably provide LBNP for up to several hours per day or any number of days per week. Based on our previous studies, 20 mmHg inside the suit was chosen for the long-term study of temperature and humidity as well as for quantifying mobility and range of motion (Fig. 1B and film clip).

Mechanical unloading of the body during spaceflight leads to musculoskeletal deconditioning.[10,28,38] While the combination of resistance and aerobic exercise countermeasure programs used on the ISS is effective in many ways, the limited space onboard future lunar and planetary spacecrafts may not allow for replication of the current suite of exercise devices,[36] so

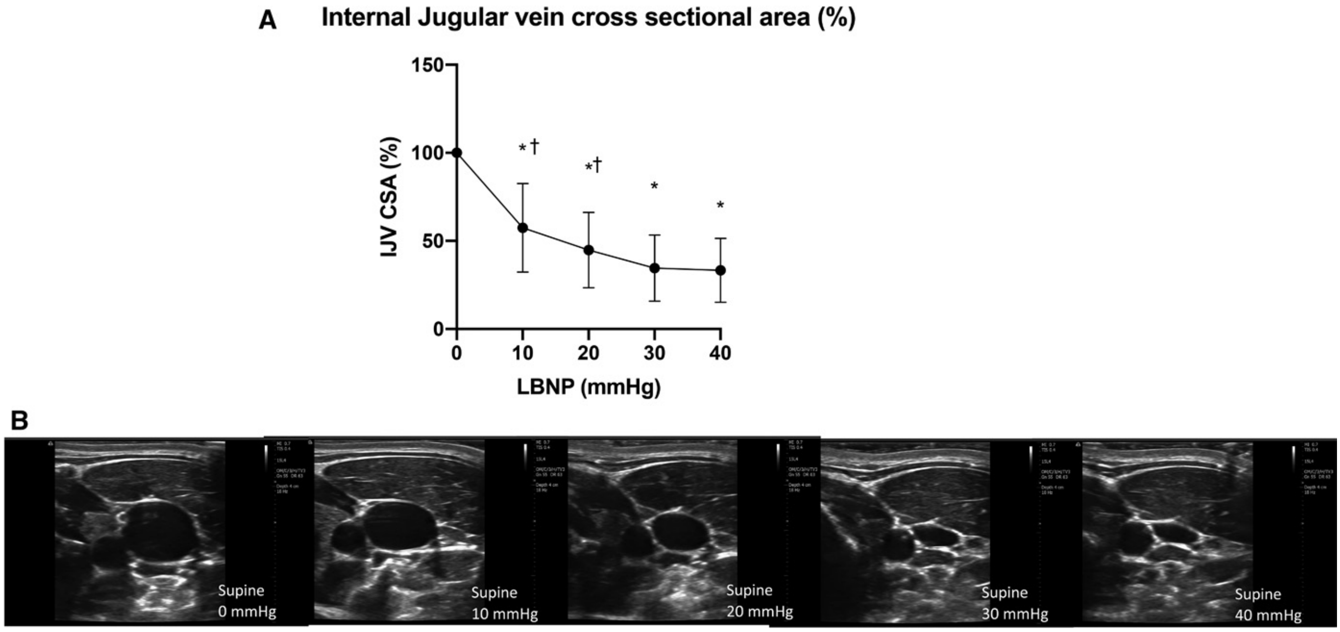

Fig. 3. Internal jugular venous cross-sectional area (IJVa). A) Reduction in IVJa in percentage from resting supine values as an indication of caudal fluid shift induced by incremental lower body negative pressure (LBNP) from 0 to 40 mmHg ($N = 8$). Values are mean ± SD. *Indicates $P < 0.05$ compared to baseline (0 mmHg of LBNP); †indicates $P < 0.05$ compared to the preceding level of LBNP. B) Ultrasound images from one subject demonstrating reduction in IVJ as a function of incremental LBNP.

methods for increasing efficacy are therefore warranted. LBNP can provide mechanical loading, which may counteract musculoskeletal deconditioning[7,20] and has, in ground-based analogs, been shown to increase efficacy of exercise.[24,30] Because the GravitySuit is flexible, it can be worn during some forms of restrictive and aerobic exercise to potentially increase efficacy. Furthermore, axial compression by virtue of the vest may hold potential benefits for spinal health.[26]

GRF generated within the flexible GravitySuit in this trial were substantially larger, at any given pressure, than observed in previous trials using a classic static and ridged LBNP-box.[14] In the flexible device, mechanical loading corresponding to full upright standing BW was achieved around 35 mmHg, which is

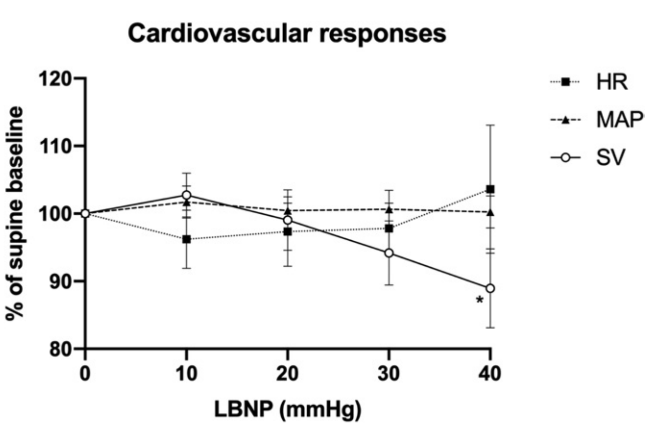

Fig. 4. Cardiovascular parameters. Heart rate (HR), mean arterial pressure (MAP), and stroke volume (SV) as a function of lower body negative pressure (LBNP) from 0–40 mmHg ($N = 8$). Values are mean ± SD. *Indicates $P < 0.05$ compared to baseline (0 mmHg of LBNP).

consistent with a flexible axially contractible device (similar to an accordion); as negative pressure is applied, the top and bottom of the device contract toward each other, thereby generating mechanical loads under the feet and on the shoulders. The resultant forces are significantly larger than historically recorded in a static LBNP box, where around 100 mmHg LBNP was needed to generate full BW loading. Additionally, previous studies were done with the subjects in a supine posture, which does not take the front-to-back (1 G_x) gravitational stress into account and thus includes friction forces between the subject and the surface they lay on. To account for this confounding factor, we used a suspension system, which also allowed for movement in all dimensions.

With increasing LBNP the variability of resulting GRF increased. As the device "collapses" the subject is able to actively push back against the soles of the shoe and the vest. The more actively the subject pushes back, the more mechanical stimulus is achieved which is likely the reason for the variability in GRF. Future testing during real weightlessness, e.g., by parabolic flight, is recommended for accurate recording of LBNP-induced mechanical loading without interference of gravitational stress along any vector.

Safety and comfort are key elements of any countermeasure device. Safety pressure-release check valves are incorporated along both feet (Fig. 1A) and open if pressure inside the suit relative to external pressure increases above a predetermined threshold; e.g., if LBNP increases above 40 mmHg, the mechanical valves will open, thereby creating a "controlled leak" and a drop in LBNP. When pressure difference is restored to 40 mmHg, the valves close and LBNP at the desired level is continued. Release-pressure threshold and thus maximum LBNP level can be adjusted and set to any level.

To increase compliance of crewmembers to wear the suit, temperature and humidity of the internal environment should be regulated; at rest the average human heat output of 350 kJ/hour, given a heat capacity of air of 1.005 kJ/(kg*K), the minimal volume flow rate to maintain temperature and humidity can be as low as 0.3 m^3/min. Two hours of LBNP during rest did not alter temperature or humidity ($N = 1$). Ongoing trials are investigating different exercise regimes in combination with the GravitySuit. By increasing power to the vacuum pump, LBNP level momentarily increases, which triggers the check valves and creates a controlled leak with substantial airflow though the suit. In this way, temperature and humidity can be controlled simply by increasing the vacuum and airflow without simultaneously increasing the LBNP-level.

Because the GravitySuit simulates some effects of gravitational stress, we suggest that use during long-term spaceflight could potentially reintroduce the diurnal variability of intracranial pressure and volume to help maintain cerebro-ocular health. Moreover, LBNP alone or in combination with exercise has shown beneficial effects on cardiovascular and musculoskeletal health, as well as better maintenance of oxidative capacity in ground-based analog studies. Simulated gravitational stress while crewmembers perform everyday tasks in flight may help maintain overall fitness and health similarly to the way everyday stress of gravity affects us on Earth. An alternative method is to apply LBNP during sleep, which is currently being tested.

The important question of "How much gravitational stress is needed to counteract the negative health effects of spaceflight?" remains unanswered. Moreover, it remains unknown if the fractional gravity of the Moon or Mars is sufficient to maintain health or keep symptoms at a subclinical level. As a future perspective, the GravitySuit could potentially be worn during stay on the surface of the Moon or Mars to augment effects of fractional gravity. Moreover, in ground-based analog trials the GravitySuit could be used to simulate fractional gravitational stress corresponding to a stay on the surface of, e.g., the Moon or Mars to further investigate physiological effects of future missions.

The mobile and flexible GravitySuit could provide a feasible method and device to apply low-level, long-term LBNP during spaceflight as an integrative countermeasure. LBNP simulates effects of gravitational stress by generating a caudal fluid shift to unload central and cranial structures while generating axial mechanical loading.

A limitation of the current study is the restricted dimensions of the suit, which only allowed for inclusion of subjects with a limited waist-, hip-, and leg-circumference and length of the legs. For this reason, we were limited in subject recruitment and primarily included women. Ongoing efforts are directed toward constructing larger size suits to test how bodyweight, surface area, and waist cross-sectional area impact the generated fluid shift and GRF. Potential implementation of the GravitySuit on the ISS, Gateway, or future spacecrafts should include different sizes to accommodate different crew, similar to the current strategy for customizing extravehicular suits.

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