RESEARCH ARTICLE

Simulations of Gravitational Stress on Normovolemic and Hypovolemic Men and Women

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Background: Earth-based simulations of physiologic responses to space mission activities are needed to develop prospective countermeasures. To determine whether upright lower body positive pressure (LBPP) provides a suitable space mission simulation, we investigated the cardiovascular responses of normovolemic and hypovolemic men and women to supine and orthostatic stress induced by head-up tilt (HUT) and upright LBPP, representing standing in lunar, Martian, and Earth gravities. ***Methods:*** Six men and six women were tested in normovolemic and hypovolemic (furosemide, intravenous, $0.5\ mg \cdot kg^{-1}$) conditions. Continuous electrocardiogram, blood pressure, segmental bioimpedance, and stroke volume (echocardiography) were recorded supine and at lunar, Martian, and Earth gravities (10°, 20°, and 80° HUT vs. 20%, 40%, and 100% bodyweight upright LBPP), respectively. Cardiovascular responses were assessed from mean values, spectral powers, and spontaneous baroreflex parameters. ***Results:*** Hypovolemia reduced plasma volume by ~10% and stroke volume by ~25% at supine, and increasing orthostatic stress resulted in further reductions. Upright LBPP induced more plasma volume losses at simulated lunar and Martian gravities compared with HUT, while both techniques induced comparable central hypovolemia at each stress. Cardiovascular responses to orthostatic stress were comparable between HUT and upright LBPP in both normovolemic and hypovolemic conditions; however, hypovolemic blood pressure was greater during standing at 100% bodyweight compared to 80° HUT due to a greater increase of total peripheral resistance. ***Conclusions:*** The comparable cardiovascular response to HUT and upright LBPP support the use of upright LBPP as a potential model to simulate activity in lunar and Martian gravities.

Keywords: blood pressure regulation, hypovolemia, baroreflex.

REDUCED PLASMA volume (PV) and altered cardiovascular regulation result from exposure to microgravity (11). Diminished blood pressure regulation following spaceflight has been attributed to reduced central plasma volume and inadequate vasoconstriction in response to the orthostatic stress imposed by return to gravity (11). To maintain adequate blood pressure (BP) and cerebral perfusion during orthostatic stress, reflex regulation is evoked by increased heart rate (HR) and vasoconstriction to compensate for reduced preload and stroke volume.

To identify physiologic responses to space mission activities so that prospective countermeasures can be developed, Earth-based simulations of human activity in fractional gravity are needed. Head-up tilt (HUT) is a widely accepted maneuver used to induce passive orthostatic stress by decreasing venous return and central blood volume accompanied by a consequent unloading of cardiopulmonary and arterial baroreceptors. However, motion restriction during HUT limits further investigation of activities in space missions. Motion restriction is not a significant problem in chambers that use lower body positive pressure (LBPP) to reduce weight bearing during upright activity (3,6). In this setting, cardiovascular responses to graded LBPP have been studied in standing men and women (6,19,20), with results indicating that body compartment fluid redistribution in response to upright posture combined with LBPP could also change preload, thereby loading or unloading both high- and low-pressure baroreceptors that regulate BP. Thus, combining upright LBPP with treadmill activity provides a way to simulate activity in reduced gravity environments with the advantage of producing a realistic environment in which subjects can perform tasks (i.e., walking, running, hill climbing, or performing directed activities) under relevant physiologic conditions (6). In addition, cardiovascular deconditioning associated with spaceflight can be simulated by pharmacologically induced hypovolemia (14).

The combination of orthostatic stress in normo- and hypovolemic men and women makes this study unique, since most studies, including our previous studies (6,16), using upright LBPP or HUT simulated only normovolemic activity. Deconditioned physiologic responses (8,15,17) to orthostatic stress have rarely been studied, especially in simulating standing on the surface of the Moon, Mars, and the Earth. The purpose of the present study was to compare cardiovascular responses between HUT and upright LBPP in both normo- and hypovolemic conditions to assess the hypothesis that upright LBPP would provide a model comparable to HUT to induce

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orthostatic stress with the advantage of freeing the subject to be active.

METHODS

Subjects

Six men (24.2 ± 0.5 yr in age, 171.8 ± 3.1 cm in height, and 74.2 ± 8.9 kg in weight) and six women (24.7 ± 0.5 yr in age, 159.1 ± 1.5 cm in height, and 59.3 ± 2.1 kg in weight), who were nonsmokers and normotensive, were recruited. None was a trained athlete. Each subject gave informed written consent to the experimental protocol, approved by the University of Kentucky Institutional Review Board for the Protection of Human Subjects and the NASA Johnson Space Center Committee for Protection of Human Subjects. Selection of subjects was based on a screening evaluation that consisted of a medical history questionnaire, a 12-lead electrocardiogram, and BP measurement.

Experimental Protocol

Each subject reported to the lab on three separate visits. During the first visit, each subject was familiarized with the protocol and with instrumentation and data collection procedures. The two subsequent visits were separated by 1 wk and occurred at the same time of day as the previous session. Subjects were studied normovolemic and hypovolemic. In the hypovolemic session, intravenous furosemide (0.5 mg · kg^{-1}, 4 mg · min^{-1}) was infused to reduce PV. Urine volume and BP were monitored for at least 2 h after the furosemide infusion to assure optimal effects, and testing started after urine output and BP were stabilized. Prior to testing, weight, height, and distance between impedance leads, resting HR, and BP of each subject were measured, and neoprene shorts (Alter G Inc., Fremont, CA) of appropriate size were donned. An antecubital vein catheter was placed for blood sample collection. Ambient temperature was maintained between 21 and 24°C.

Head-up tilt protocol: The HUT protocol involved moving the subjects from supine to 10°, 20°, and 80° HUT in a graded manner with an electric tilt table to simulate passive standing in lunar, Martian, and Earth gravity, respectively. The HUT trial began with subjects lying supine on the table while ultrasonic images of the heart (~10 min) and noninvasive cardiovascular measurements (3 min) were made. The same procedure was repeated at each of the three tilt angles.

Upright lower body positive pressure protocol: Testing was conducted using a commercially available LBPP chamber with an enclosed treadmill (G Trainer, Alter G, Inc.). The upright LBPP protocol included applications of positive pressure to subjects in the upright posture to reduce bodyweight (BW) to 20% and 40%, or remain at 100% BW (standing without a significant amount of LBPP) to simulate effects of lunar, Martian, and Earth gravity, respectively. The upright LBPP test began by standing upright with legs and hips sealed in the chamber. Ultrasound (~10 min) and noninvasive cardiovascular measurements (3 min) were conducted at each BW.

The order of HUT and upright LBPP testing was randomized among subjects, but the same order of HUT and LBPP was used in both normo- and hypovolemic tests for a given person. If orthostatic hypotension symptoms developed (systolic blood pressure below 70 mmHg, HR drop greater than 20 bpm, lightheadness, dizziness, or nausea), the HUT or upright LBPP test was terminated immediately. Subjects were de-instrumented and fed salty snacks and drinks after all tests were completed. The medical monitor was in charge of assessment of cardiovascular recovery and dismissal of subjects at the end of the study.

Blood samples: In both normo- and hypovolemic conditions, a blood sample was collected from an intravenous antecubital catheter at the end of each stress for subsequent analysis of hematocrit (Hct) and hemoglobin (Hb). The percentage changes in PV with furosemide administration and with orthostatic stresses were calculated using Hct and Hb (9).

Instrumentation and Data Acquisition

Standard lead II electrocardiogram (SpaceLab, Snoqualmie, WA) was continuously monitored and collected. Continuous BP and HR were obtained at the finger using photoplethysmography (Portapres, Finapres Medical Systems, Amsterdam, The Netherlands) with the hand positioned at heart level. Brachial artery BP was measured periodically using a manometer (UA-767, A&D Medical, San Jose, CA) placed around the upper arm for the calibration of continuous BP. Stroke volume (SV) was recorded with a pulsed wave Doppler probe (Philips, Andover, MA). A tetra-polar high resolution impedance meter (UFI Model 2994D, Morro Bay, CA) was used to measure body segmental fluid shifts. The angle of the tilt table was recorded by an accelerometer (Crossbow, Jameco, CA) and pressure in the LBPP chamber was measured by an air pressure transducer (CyQ 301, CyberSense, Nicholasville, KY). All data were collected by computer acquisition software (WinDAQ, DATAQ Instruments, Akron, OH) at 1000 Hz with subsequent analysis of mean, spectral power and baroreflex function using MATLAB (Mathworks, Natick, MA).

Data Analysis

Mean values: Heart rate and RR intervals were computed by identifying R waves in the last 3 min of each data segment. Artifacts in the HR and BP signals were removed manually. Systolic (SBP) and diastolic (DBP) blood pressures were determined by computing the maximum and minimum values of BP for each heartbeat and were used to calculate mean arterial blood pressure (MAP, equals to two-thirds DBP plus one-third SBP). Estimates of total peripheral resistance (TPR) were calculated as MAP/cardiac output (CO). Mean values were computed for each 3-min time segment.

Spectral power: RR interval, SBP, and DBP were resampled at 4 Hz using a cubic spline method. Each data segment was then linearly detrended. Power spectral densities (PSD) of these variables were estimated using

Welch's method of averaged periodograms (480-point Hamming window with 440-point overlap). Spectral powers (24) in low (LF, 0.04–0.15 Hz) and high (HF, 0.15–0.40 Hz) frequency regions were obtained using trapezoidal integration over the specified frequency ranges.

Baroreflex sequences: A sequence method (1) was used to provide information about the number of blood pressure ramps, the number of baroreflex sequences, baroreflex sensitivity, and baroreflex effectiveness. Sequences of three or more consecutive heartbeats in which progressively increasing or decreasing SBP (at least 1 mmHg) were followed by progressively lengthening or shortening of RR intervals (no less than 4 ms) were identified. A sequence was accepted as a baroreflex sequence if the correlation coefficient of the regression line between SBP and RR interval within the sequence was no less than 0.85 (1). Spontaneous baroreflex sensitivity (BRS) was defined as the slope of the regression line for each sequence. The ratio between the number of baroreflex sequences and the total number of SBP ramps determined the baroreflex effectiveness index (BEI) (4). For each subject, the numbers of SBP ramps and baroreflex sequences were normalized by the number of analyzed heartbeats in each data segment since both parameters depend on the number of analyzed heartbeats, which varied within and among subjects.

Statistics: Variables were compared using a mixed model analysis of variance (ANOVA) with Condition (normo- and hypovolemia) × Stage (simulated gravitational environment of spaceflight, Moon, Mars, and Earth) × Technique (HUT and upright LBPP) for main effects and interactions. Significant interaction with Technique was considered most relevant for assessing the differential effect of HUT and upright LBPP. When significant effects were observed, Tukey's post hoc analysis was performed to estimate differences in pairwise comparisons. Significance was accepted at $P < 0.05$. Analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC). Results are presented as mean ± SEM.

RESULTS

Complete data were collected from all normovolemic subjects. We collected no data from one man in the hypovolemic condition since his BP was above 140/90 mmHg. The incidence of presyncope prevented collection of complete data segments from some hypovolemic subjects. Specifically, we did not collect data from three other hypovolemic subjects at 100% BW and two at 80° HUT. Subjects experienced presyncope in 3 (all during HUT) out of 24 tests in the normovolemic conditions and in 13 (8 during HUT, and 5 during LBPP) out of 20 tests in the hypovolemic conditions. The level of LBPP required to reduce a subject's bodyweight was not different in the normo- and hypovolemic conditions (33.7 ± 1.7 vs. 31.6 ± 0.9 mmHg for 20% BW and 25.4 ± 1.3 vs. 24.0 ± 0.7 mmHg for 40% BW).

Table I shows average values of steady state hemodynamics at supine and in response to upright LBPP and HUT in both the normo- and hypovolemic conditions. Compared with the normovolemic condition, dehydration increased Hct (main effect of Condition, $P < 0.0001$) and Hb (main effect of Condition, $P < 0.0001$), resulting in a 9.5 ± 1.3% decrease of resting PV (main effect of Condition, $P < 0.0001$). This hypovolemia was accompanied by significant reductions in SV (main effect of Condition, $P < 0.0001$) and CO (main effect of Condition, $P < 0.0001$). Dehydration increased HR at simulated lunar ($P = 0.0008$), Martian ($P = 0.0002$), and Earth ($P < 0.0001$) gravities, but had no significant effect on resting HR ($P = 0.4576$) or resting BP ($P = 0.3940$, 0.1909, 0.5120 for SBP, DBP, and MAP, respectively).

Compared with supine rest, increasing orthostatic stress induced by HUT or upright LBPP elevated HR (Condition × Stage interaction, $P = 0.0003$) and reduced SV (main effect of Stage, $P < 0.0001$), with the result that CO was maintained. Hct (Technique × Stage interaction, $P = 0.0004$) and Hb (Technique × Stage interaction, $P = 0.0006$) were increased, while PV (Technique × Stage interaction, $P < 0.0001$) was decreased by both HUT and upright LBPP. Compared with HUT, higher Hct and Hb, and greater PV loss were observed at simulated lunar ($P < 0.0001$ for Hct, Hb, and PV loss) and Martian ($P = 0.0309$ for Hct, $P = 0.0077$ for Hb, and $P < 0.0001$ for PV loss) gravities during upright LBPP. Compared with supine rest, SBP (Technique × Stage interaction, $P < 0.0001$) was reduced by HUT and reached significance at 80° ($P < 0.0001$), but DBP and MAP (**Fig. 1**) were maintained during HUT in both conditions. During upright LBPP, SBP was maintained at supine values in both conditions; however, DBP was significantly increased at 20% ($P = 0.0027$) and 40% BW ($P = 0.0333$) in the normovolemic condition and at 20% ($P = 0.0497$), 40% ($P = 0.0422$), and 100% BW ($P < 0.0001$) in the hypovolemic condition. MAP was maintained at supine values in both conditions during upright LBPP, except at 100% BW in the hypovolemic condition ($P < 0.0001$), when it was significantly elevated. Hypovolemia resulted in increased DBP ($P = 0.0471$) and MAP ($P = 0.0111$) at 100% BW, but had no significant effect on BP responses at other stages. Significantly higher BP responses were observed during upright LBPP compared to HUT at Earth's gravity in both normo- ($P < 0.0001$ for SBP, $P = 0.0380$ for DBP, and $P = 0.0072$ for MAP) and hypovolemic ($P < 0.0001$ for SBP, MAP, and DBP) conditions. Compared with supine, TPR appeared to increase with upright LBPP and HUT (main effect of stage, $P = 0.0350$), but a post hoc analysis indicated the increase was not significant even at Earth gravity ($P = 0.0557$). Higher TPR was observed during upright LBPP than during HUT (main effect of technique, $P = 0.0069$).

Segmental impedance indicated that furosemide infusion induced significant central hypovolemia (main effect of condition, $P < 0.0001$) and both HUT and upright LBPP led to equivalent central fluid loss (**Fig. 2**, main effect of Technique, $P = 0.5718$), and equivalent fluid loss in the upper leg (not shown, main effect of Technique, $P = 0.1316$). However, upright LBPP induced greater fluid pooling in the abdominal region (Fig. 2,

TABLE I. STEADY STATE CARDIOVASCULAR RESPONSES TO SUPINE REST AND ORTHOSTATIC STRESSES INDUCED BY HEAD-UP TILT AND UPRIGHT LOWER BODY POSITIVE PRESSURE IN NORMO- (SIX MEN AND SIX WOMEN) AND HYPOVOLEMIC (FIVE MEN AND SIX WOMEN) CONDITIONS.

	Baseline	Head-Up Tilt			Upright Lower Body Positive Pressure		
	Supine	**HUT 10°**	**HUT 20°**	**HUT 80°**	**20% BW**	**40% BW**	**100% BW**
Heart rate, bpm							
Normovolemia	64 ± 3	63 ± 3	64 ± 3	82 ± 3*	65 ± 3	68 ± 2	80 ± 2*
Hypovolemia	65 ± 2	67 ± 3†	70 ± 3†*	93 ± 5†*	71 ± 3†*	74 ± 3†*	93 ± 5†*
Systolic blood pressure, mmHg							
Normovolemia	116 ± 4	113 ± 4	112 ± 4	104 ± 4*	118 ± 4	115 ± 4	114 ± 4‡
Hypovolemia	112 ± 4	109 ± 4	108 ± 3	99 ± 4*	112 ± 3	109 ± 2	120 ± 7‡
Diastolic blood pressure, mmHg							
Normovolemia	71 ± 2	70 ± 2	69 ± 3	70 ± 3	79 ± 2*‡	78 ± 3*‡	77 ± 3‡
Hypovolemia	69 ± 2	70 ± 2	69 ± 3	69 ± 3	76 ± 2*	76 ± 2*	84 ± 2†*‡
Mean arterial pressure, mmHg							
Normovolemia	86 ± 3	84 ± 3	84 ± 3	82 ± 3	92 ± 3‡	90 ± 3‡	90 ± 3‡
Hypovolemia	83 ± 3	83 ± 2	82 ± 3	79 ± 3	88 ± 2	87 ± 2	96 ± 4†*‡
Stroke volume, ml							
Normovolemia	65 ± 4	64 ± 4	61 ± 4*	47 ± 3*	61 ± 3	54 ± 2*	44 ± 2*
Hypovolemia	50 ± 5†	49 ± 4†	44 ± 4†*	36 ± 3†*	49 ± 4†	42 ± 4†*	35 ± 3†*
Cardiac output, $L \cdot min^{-1}$							
Normovolemia	3.85 ± 0.27	3.80 ± 0.27	3.67 ± 0.25	3.50 ± 0.21	3.86 ± 0.17	3.32 ± 0.15	3.23 ± 0.17
Hypovolemia	3.04 ± 0.20†	2.97 ± 0.18†	2.91 ± 0.16†	3.01 ± 0.23†	3.10 ± 0.22†	2.94 ± 0.21†	2.99 ± 0.21†
Total peripheral resistance, $mmHg \cdot (L \cdot min^{-1})^{-1}$							
Normovolemia	25.3 ± 1.4	23.2 ± 1.5	23.8 ± 1.6	24.1 ± 1.3	24.4 ± 1.3‡	27.6 ± 1.1‡	28.4 ± 1.5‡
Hypovolemia	28.7 ± 2.4†	28.8 ± 1.8†	29.3 ± 2.3†	29.4 ± 2.5†	29.8 ± 2.2†‡	31.3 ± 2.9†‡	33.0 ± 2.7†‡
Hemoglobin, $g \cdot dl^{-1}$							
Normovolemia	13.6 ± 0.4	13.8 ± 0.4	13.8 ± 0.4	14.6 ± 0.4*	14.4 ± 0.4*‡	14.3 ± 0.4*‡	14.5 ± 0.4*
Hypovolemia	14.6 ± 0.4†	14.7 ± 0.4†	14.8 ± 0.4†	15.2 ± 0.4†*	15.1 ± 0.4†*‡	15.1 ± 0.4†*‡	15.1 ± 0.5†*
Hematocrit, %							
Normovolemia	39.3 ± 1.1	39.7 ± 1.2	40.0 ± 1.2	41.9 ± 1.2*	41.6 ± 1.2*‡	41.2 ± 1.2*‡	41.8 ± 1.1*
Hypovolemia	42.2 ± 1.1†	42.3 ± 1.1†	42.6 ± 1.1†	43.9 ± 1.1†*	43.8 ± 1.0†*‡	43.5 ± 1.1†*‡	43.5 ± 1.4†*
Plasma volume percentage change with respect to supine normovolemia, %							
Normovolemia	0	−1.5 ± 0.8	−2.5 ± 0.7	−10.5 ± 0.6*	−8.8 ± 1.0*‡	−7.7 ± 1.0*‡	−10.2 ± 0.8*
Hypovolemia	−9.5 ± 1.3†	−9.9 ± 1.2†	−10.9 ± 1.2†	−16.3 ± 1.4†*	−15.9 ± 1.1†*‡	−15.0 ± 1.3†*‡	−16.3 ± 1.5†*

Values are mean ± SEM. †Significantly different from normovolemia at the same stage, $P < 0.05$; *significantly different from supine rest in the same condition using the same technique, $P < 0.05$; ‡significantly different from head-up tilt response at matched level of orthostatic stress in the same condition, $P < 0.05$.

main effect of Technique, $P = 0.0002$) and lower leg (not shown, main effect of Technique, $P = 0.0001$) than did HUT.

Table II shows regulatory cardiovascular responses to HUT and upright LBPP in normo- and hypovolemic conditions. Compared with normovolemia, hypovolemia resulted in increased low-frequency diastolic blood pressure oscillations (DBP_{LF}, main effect of Condition, $P = 0.0178$), increased TPR (main effect of Condition, $P < 0.0001$, Table I), reduced BRS (main effect of Condition, $P < 0.0001$), and increased BEI (main effect of Condition, $P < 0.0001$), resulting from a significant increase in the number of baroreflex sequences in combination with no change in the number of BP ramps (not shown). The ratio of low- to high-frequency RR interval oscillations ($RR_{LF/HF}$) was increased (main effect of Condition, $P = 0.0184$) by dehydration. Normalized high-frequency (by low- and high-frequency power) RR interval oscillations (RR_{HFnu}) were not different for normo- and hypovolemic conditions at supine, but were reduced by hypovolemia at simulated lunar ($P = 0.0472$), Martian ($P = 0.0004$), and Earth ($P = 0.0402$) gravities.

Compared with supine, Earth's gravity simulated by both upright LBPP and HUT resulted in significantly reduced BRS ($P < 0.0001$) and increased BEI ($P < 0.0001$), $RR_{LF/HF}$ ($P < 0.0001$), and DBP_{LF} ($P < 0.0001$) in both conditions. Significantly reduced supine RR_{HFnu} was observed at 80° HUT and 100% BW upright LBPP ($P < 0.0001$) in the normovolemic condition. Significantly reduced supine RR_{HFnu} was also observed at Martian ($P = 0.0012$) and Earth ($P < 0.0001$) gravities simulated by both HUT and upright LBPP in the hypovolemic condition.

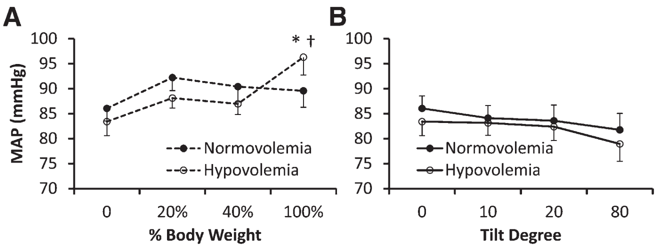

Fig. 1. Mean arterial pressure (MAP) in normo- and hypovolemic conditions plotted as a function of increasing orthostatic stress evoked by A) upright LBPP and B) HUT. †Significantly different from normovolemia at the same stage, $P < 0.05$; *significantly different from baseline in the same condition, $P < 0.05$.

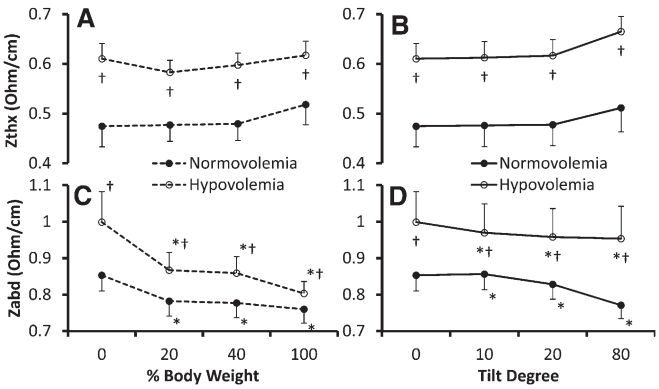

Fig. 2. Normalized (by distance between electrodes) thoracic impedance (Zthx) in normo- and hypovolemic conditions plotted as a function of increasing orthostatic stress evoked by A) upright LBPP and B) HUT. Normalized (by distance between electrodes) abdominal impedance (Zabd) in normo- and hypovolemic conditions plotted as a function of increasing orthostatic stress evoked by C) upright LBPP and D) HUT. †Significantly different from normovolemia at the same stage, $P < 0.05$; * significantly different from baseline in the same condition using the same technique, $P < 0.05$.

DISCUSSION

Cardiovascular responses were compared between upright LBPP and HUT in normo- and hypovolemic men and women. The primary findings were: 1) there was no difference between upright LBPP and HUT with respect to changes of numerous cardiovascular indices, including HR, SV, CO, $RR_{LF/HF}$, RR_{HFnu}, BRS, BEI, TPR, and DBP_{LF} in response to orthostatic stress and hypovolemia; 2) upright LBPP induced greater PV loss at simulated lunar and Martian gravities compared to matched levels of HUT; and 3) although similar blood pressures were observed in response to orthostatic stress in the normovolemic condition, blood pressures increased during standing at 100% BW, but not during 80° HUT when hypovolemic.

Increased orthostatic stress is known to induce blood pooling in the lower body, leading to reduced central blood volume and venous return (21), as indicated by decreasing SV and increasing thoracic impedance in our study. Increasing tilt angle or decreasing LBPP unloads cardiopulmonary baroreceptors and reduces the inhibition of arterial baroreceptors (6,20) to increase HR to maintain CO near supine values. It is widely accepted that the HF power of RR intervals is mediated predominantly by changes in vagal activity, while LF power is determined by changes in both sympathetic and vagal activity (18). Therefore, the increased $RR_{LF/HF}$ and decreased RR_{HFnu} associated with increased HR may indicate an enhancement of sympathetic activity and a shift of sympathovagal balance toward sympathetic control. The increased DBP_{LF} may indicate increased activation of reflex-mediated sympathetic pathways to peripheral vasculature since LF power of DBP oscillations has been shown to be related to vasomotor activity based on group mean (22). In addition, the increase in BEI with increasing orthostatic stress indicated increased effectiveness of baroreceptors driving the sinus node, while reduced BRS suggested that the strength of the baroreflex was diminished (4). Furosemide administration induced a PV loss comparable to the hypovolemia occurring after short-term microgravity exposure (11). As a result, a greater SV reduction was observed and a higher HR response was evoked at each stress following dehydration. The higher HR was associated with smaller RR_{HFnu} and greater $RR_{LF/HF}$, indicating inhibition of parasympathetic activity by the dehydration procedure. Dehydration also appeared to enhance sympathetic vasomotor activity (14,15) and reduce baroreflex strength (14) since hypovolemia led to an increase in DBP_{LF} and a reduction in BRS.

Diminished ability to maintain BP in response to orthostatic stress may result in orthostatic hypotension.

TABLE II. NEURALLY MEDIATED REGULATORY RESPONSES TO SUPINE REST AND ORTHOSTATIC STRESSES INDUCED BY HEAD-UP TILT AND UPRIGHT LOWER BODY POSITIVE PRESSURE IN NORMO- (SIX MEN AND SIX WOMEN) AND HYPOVOLEMIC (FIVE MEN AND SIX WOMEN) CONDITIONS.

	Baseline	Head-Up Tilt			Upright Lower Body Positive Pressure		
	Supine	HUT 10°	HUT 20°	HUT 80°	20% BW	40% BW	100% BW
Ratio of low to high frequency RR interval oscillations, a.u.							
Normovolemia	1.5 ± 0.5	1.0 ± 0.2	1.4 ± 0.3	8.2 ± 2.2*	1.8 ± 0.4	1.6 ± 0.3	8.0 ± 2.5*
Hypovolemia	1.4 ± 0.3†	1.8 ± 0.3†	2.2 ± 0.4†	13.8 ± 4.9†*	3.5 ± 1.3†	4.1 ± 1.3†	10.7 ± 1.9†*
Normalized high frequency RR interval oscillations, a.u.							
Normovolemia	0.43 ± 0.05	0.53 ± 0.04	0.47 ± 0.04	0.16 ± 0.03*	0.43 ± 0.05	0.44 ± 0.04	0.21 ± 0.05*
Hypovolemia	0.47 ± 0.05	0.39 ± 0.04†	0.37 ± 0.05†*	0.11 ± 0.02†*	0.41 ± 0.08†	0.28 ± 0.05†*	0.10 ± 0.02†*
Low frequency spectral power of diastolic blood pressure, $mmHg^2$							
Normovolemia	2.5 ± 0.5	2.6 ± 0.5	3.4 ± 0.8	5.4 ± 1.0*	3.5 ± 0.8	3.3 ± 0.5	5.4 ± 1.3*
Hypovolemia	3.2 ± 0.5†	3.0 ± 0.7†	4.1 ± 0.8†	7.2 ± 1.9†*	5.2 ± 1.6†	3.5 ± 1.0†	9.4 ± 2.5†*
Arterial baroreflex sensitivity, ms/mmHg							
Normovolemia	26.9 ± 4.1	21.6 ± 3.5	27.8 ± 4.6	13.5 ± 2.3*	29.0 ± 5.7	22.9 ± 4.4	12.6 ± 2.0*
Hypovolemia	23.5 ± 2.7†	20.6 ± 3.1†	21.6 ± 3.5†	7.2 ± 1.7†*	14.8 ± 1.7†	18.4 ± 2.6†	8.7 ± 1.5†*
Baroreflex effectiveness index, a.u.							
Normovolemia	0.23 ± 0.05	0.28 ± 0.07	0.25 ± 0.05	0.49 ± 0.05*	0.21 ± 0.04	0.25 ± 0.04	0.43 ± 0.04*
Hypovolemia	0.29 ± 0.05†	0.41 ± 0.05†	0.42 ± 0.06†	0.51 ± 0.06†*	0.30 ± 0.05†	0.39 ± 0.05†	0.52 ± 0.07†*

Values are mean ± SEM. †Significantly different from normovolemia at the same stage, $P < 0.05$; *significantly different from supine rest in the same condition using the same technique, $P < 0.05$.

One factor in the development of orthostatic hypotension may be the inability of subjects to adequately elevate their peripheral resistance (5). The greater TPR during upright LBPP may contribute to the reduced incidence of orthostatic intolerance compared to HUT. It is unlikely that reflex-mediated vasomotion contributed to the difference of TPR since DBP_{LF} was comparable between the two techniques, so local mechanisms need to be considered as those may intervene in baroreflex regulation (7). Several studies (7,23) have suggested that an increase in intramuscular pressure can reflexively increase BP. The higher TPR may result from mechanical compression of the vasculature in the lower body during upright LBPP, signaled via the intramuscular mechanoreflex (7,20,23). Also, as indicated by greater blood pooling in the lower body, greater lower body transmural pressure existed during upright LBPP compared to HUT. Henriksen (12) observed that the venoarterial reflex was activated when transmural pressure exceeded 25 mmHg and, therefore, might contribute to the higher TPR in upright LBPP due to greater venous distension. In addition, transmural pressure increased with increasing orthostatic stress and was greater during upright LBPP compared to HUT at each stress level. So the myogenic response, in which vasoconstriction occurs when transmural pressure increases, might be greater in the arteries of the leg in upright LBPP than in HUT. After dehydration, although both DBP_{LF} and TPR were elevated, the reduction in PV appears to have been the primary reason for the increased incidence of orthostatic intolerance.

In the present study, differential effects of upright LBPP and HUT were observed in Hct, Hb, PV change, and BP responses. Comparable PV losses (Hct and Hb elevations) were observed at 80° HUT and 100% BW upright LBPP. Compared with standing, decreasing tilt angle preserved PV, while increasing LBPP had no significant effect to prevent PV loss, which led to greater PV losses at simulated lunar and Martian stresses in upright LBPP compared with HUT. Other studies have reported that 60 mmHg LBPP prevented PV reduction during 60° HUT in men (13) and in standing men and women (17), respectively. However, in both studies (13,17), the abdominal compartment was compressed by the antigravity suit that employed five bladders to provide positive pressure and the compression was applied either before tilting up (13) or for an extend time period (1 h) (17). In our study, a maximum chamber pressure of less than 40 mmHg was applied for ~15 min, the abdominal compartment was not compressed, and LBPP was not applied before standing. We speculate that increasing LBPP induced fluid pooling in the abdominal compartment, resulting in increased filtration at this vulnerable site in our study. It has been known that as hydrostatic pressure increased with upright posture, capillary filtration into the interstitial space increased, thereby reducing PV (10). Reduced filtration with reducing tilt angle and increased filtration with increasing chamber pressure may contribute to the different effects of upright LBPP and HUT at intermediate stresses.

Dehydration changed BP responses to upright LBPP but not to HUT. In the normovolemic condition, application of LBPP resulted in nonsignificant increases of standing SBP, DBP, and MAP, which are consistent with our previous study (6) and others (3). However, Shi et al. (23) indicated that supine MAP increased by 3-6 mmHg at 20-30 mmHg LBPP and by 4-15mmHg at 40-50 mmHg LBPP. The relatively small BP responses to LBPP observed in our study may be due to upright posture, as indicated by Nishiyasu and associates (19,20), who determined that BP response to LBPP was dependent on body position. In the hypovolemic condition, we observed a significant elevation of DBP and MAP at 100% BW. These BP findings are not without precedent. Kimmerly et al. (15) demonstrated augmented MAP at −40 mmHg lower body negative pressure in hypovolemic subjects and attributed this to enhanced sympathetically mediated arterial baroreflex responses and an upward shift of cardiopulmonary baroreflex sensitivity. A normal rise in TPR and DBP_{LF} despite increased BP at 100% BW during hypovolemia suggests that sympathetic vasomotor responses to orthostasis may have been enhanced in this dehydrated condition during upright standing.

A limitation was that different LBPPs were used for each subject to reduce BW to 20% and 40%, respectively, since the surface area of the waist seal of this commercially available device was constant. The technique that Boda et al. (2) used, radially changing the surface area of the waist seal to expose each subject to the same pressure, could eliminate this limitation. Also, our determination of sympathetic activity was indirect (22), but results from direct measurements of sympathetic nerve activity in similar studies (7,8) support our results.

In conclusion, the study documents cardiovascular responses to HUT and upright LBPP in terms of standing in lunar, Martian, and Earth gravities in normo- and hypovolemic conditions. Several cardiovascular responses were similar between HUT (10° and 20°) and upright LBPP (20% and 40% BW), which supports the use of upright LBPP as a potential model to simulate activity in fractional gravity. The normal rise in DBP_{LF} and TPR despite increased BP at 100% BW in the hypovolemic condition indicates that dehydration may enhance the sympathetic vasomotor response to orthostasis.

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