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Leg Vascular Responsiveness During Acute Orthostasis Following Simulated Weightlessness

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Ten men (35-49 years old) underwent lower body negative pressure (LBNP) exposures before and after 10 d of continuous 6° head-down bedrest in order to predict the effect of weightlessness on the responsiveness of leg vasculature to an orthostatic stress. Heart rate (HR), mean arterial blood pressure (MAP), and impedance rheographic indices of arterial pulse volume (APV) of the legs were measured during rest and at 1 min of -30 mm Hg LBNP. Bedrest-induced deconditioning was manifested by decreases ($p < 0.05$) in plasma volume (17%), peak oxygen uptake (16%), and LBNP tolerance (17%). Resting HR was unchanged after bedrest, but HR was higher ($p < 0.05$) at 1 min of -30 mm Hg LBNP after, compared with before, bedrest. Responses of MAP to -30 mm Hg LBNP were not altered by bedrest. Resting APV was decreased ($p < 0.05$) by simulated weightlessness. However, APV was reduced ($p < 0.05$) from rest to 1 min -30 mm Hg LBNP by the same relative magnitude before and after bedrest ($-21.4 \pm 3.4\%$ and $-20.5 \pm 2.7\%$, respectively). We conclude that peripheral arterial vasoconstriction, as indicated by reductions in APV during LBNP, was not affected by bedrest. These results suggest that there was no apparent alteration in responsiveness of the leg vasculature following simulated weightlessness. Therefore, it appears unlikely that control mechanisms of peripheral resistance contribute significantly to reduced orthostatic tolerance following spaceflight.

CARDIOVASCULAR ADAPTATION to weightlessness occurs in manned spaceflight as well as in ground-based simulation of microgravity (2,3,10,18-20). Adaptation is accompanied by hypovolemia and orthostatic intolerance on return to Earth's normal gravitational forces. In

an effort to understand the cause of deficient blood pressure regulation during orthostasis at 1 G following prolonged exposure to microgravity, investigators have sought possible alterations in control mechanisms of cardiac and peripheral hemodynamics. Data pertaining to alterations in cardiovascular function after bedrest (simulated weightlessness) and actual spaceflight are inconclusive. Identification of defects in the control of peripheral vascular resistance during orthostasis after prolonged weightlessness might explain the orthostatic intolerance observed in astronauts following spacecraft reentry to the Earth's gravitational environment.

Orthostasis causes blood to be pooled in the lower extremities (1,13,15). Adequate control of leg vasculature is essential for maintenance of arterial pressure following exposure to weightlessness (2). Some investigators have suggested that arterial and venous functions may be impaired following adaptation to hypogravity (7,17,21). For example, hemodynamics of the legs may change following weightlessness; this could be evident in alteration of vascular smooth muscle response to adrenergic stimulation during orthostatic stress. We examined changes in the arterial pulse volume (APV) of the legs during exposure to lower body negative pressure (LBNP) as an index of the vascular response to orthostatic stress before and after simulated weightlessness. We did this in order to test the hypothesis that smooth muscle responsiveness would decrease in the arterial vasculature (7) following simulated weightlessness.

METHODS

Ten healthy men with a mean (\pm S.E.) age of 39 ± 2 years (range 35-49), a mean height of 178 ± 2 cm (range 168-185), and a mean weight of 74.17 ± 2.47 kg (range 64.04-92.87) gave written consent to participate as volun-

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teers. Subject selection was based on normal clinical results of a screening evaluation consisting of a detailed physical examination including a maximal treadmill stress test, a pulmonary function test, a chest X-ray, complete blood count, and urinalysis. No subject was taking medication at the time of the study, and alcohol, caffeine, and exercise were not allowed during the study.

Subjects spent 1 month undergoing familiarization testing for all experimental procedures. The experiment included a 1-week ambulatory control period, followed by 10 d of 6° head-down bedrest. All tests were conducted between 0730 and 1400 hours.

Subjects were exposed to LBNP on the third to sixth days preceding bedrest and again at the end of bedrest. A 7-ml blood sample was drawn from the antecubital vein of each subject after instrumentation and placement into the plexiglass LBNP apparatus. After a 5-min supine resting control period (PreLBNP), each subject underwent a graded LBNP tolerance test. LBNP was first applied for 3-min at -30 mm Hg, then -50 mm Hg for 5-min, and finally, additional increments of -10 mm Hg for 5-min each to a maximal pressure of -100 mm Hg or test termination. The temperature inside the LBNP chamber was constant throughout the experiment. The criteria for test termination were: a) completion of 5-min at -100 mmHg; b) onset of presyncope symptoms as indicated by a sudden bradycardia greater than 15 bpm and/or a precipitous fall in systolic blood pressure greater than 15 mm Hg between adjacent 30-s measurements; c) progressively decreased systolic blood pressure to below 80 mm Hg; or d) voluntary subject termination due to discomfort such as nausea or dizziness. Peak LBNP tolerance was defined as the total time (in minutes) of exposure to decompression prior to test termination. For comparison of hemodynamic responses before and after simulated weightlessness, we analyzed only measurements taken 1 min after initiating -30 mm Hg LBNP because this was the longest exposure completed by all subjects before and after bedrest.

Measurements of pulse resistances within the midhigh leg segment were made during rest and 1-min after initiation of LBNP at -30 mm Hg. Subject instrumentation for these measurements was as follows: a) electrodes were attached to the foot, ankle, and midhigh region of each leg; b) additional spot electrodes were attached to the right and left shoulders; c) the right and left leg and shoulder electrodes were connected to form parallel segments; and d) multiple length and circumference measurements were recorded between the midhigh and ankle electrodes which defined the leg segment.

Indices of arterial pulse volume (APV) were measured with a tetra-polar impedance plethysmograph (a modified Beckman BR-100 Impedance Rheograph). The impedance rheograph introduced a high frequency (100.4 kHz), low amperage (0.7 mA R.M.S.) constant electrical current between the shoulder and foot electrodes. Simultaneous baseline resistance and pulse resistance changes were measured in the parallel leg segments between the ankle and midhigh electrodes. Impedance measurements of baseline and pulse resistances have shown proportionality to limb volumes and APV, respectively (16). This impedance technique has demonstrated a high correlation ($r = 0.995$) with the Whitney strain plethysmographic method (12). The pulse resistance

measurements were used to calculate a mean APV, which represented the average amount of blood that entered the segment during each heartbeat and was used as an index of the degree of arterial constriction (15,16). The percent change of APV from rest to 1-min of LBNP exposure at -30 mm Hg was used to compare peripheral vascular responses before and after simulated weightlessness.

Heart rate was measured continuously during the LBNP test with a Hewlett Packard monitor (model 78203A). Systolic (SBP) and diastolic (DBP) blood pressures were recorded each 30-s of the LBNP test with an L.M. Electronics automated system (model BAA-40W). Microphone recordings of Korotkoff sounds I and IV were superimposed upon a calibrated descending brachial cuff ramp. These sounds were transcribed to identify systolic and diastolic blood pressures, respectively. Mean arterial pressure (MAP) was calculated by dividing the sum of SBP and twice DBP by three.

On the day preceding bedrest and at the end of bedrest, each subject exercised in a supine posture up to peak level of oxygen uptake. A Collins electronic cycle ergometer was rotated backward 90° and attached to a ventilated exercise bed that allowed nearly complete exposure of skin for evaporative heat loss. Exercise consisted of a 3-min warmup at zero watts followed by 15-W increments in load each minute up to a self-determined endpoint of fatigue. Subjects breathed through an Otis-McKerrow respiratory valve, while the volume of expired gases was measured with a Parkinson-Cowan high-velocity, low-resistance flowmeter. Expired gas samples were drawn from a mixing chamber and analyzed for oxygen and carbon dioxide with a Perkin-Elmer mass spectrometer. Oxygen uptake was measured at 30-s intervals in all exercise tests.

Body fat was determined by underwater densitometry (11) on day 7 of the prebedrest control period and at the end of bedrest. Plasma volume was measured before and after bedrest using a modified Evans blue dye dilution method (8). Total blood volume was calculated from hematocrit and plasma volume measurements. The blood drawn prior to LBNP was analyzed for plasma norepinephrine by the technique described by Henry *et al.* (9).

The data were analyzed with two-way analysis of variance and two-tailed paired t-test statistics. The null hypothesis was rejected when p values were less than 0.05.

RESULTS

Adaptations to 10 d of simulated weightlessness are presented in Table I. Mean body weight and body fat were unaffected by bedrest. Peak oxygen uptake was reduced by

TABLE I. ADAPTATIONS TO SIMULATED WEIGHTLESSNESS.

Variable	PreBR	PostBR
Total Body Weight, kg	74.9 ± 2.5	74.8 ± 2.3
Body Fat Content, kg	13.0 ± 1.1	13.5 ± 1.1
Plasma Volume, ml	3407 ± 126	2862 ± 103*
Blood Volume, ml	5646 ± 207	4847 ± 186*
Resting Plasma NE, pg/ml	189 ± 15	232 ± 36
Peak Oxygen Uptake, L·min ⁻¹	2.84 ± .18	2.40 ± .14*
LBNP Tolerance, min	13.4 ± 1.4	9.8 ± 1.6*

Values are mean ± S.E.

* $p < 0.05$ vs. pre bedrest.

TABLE II. MEAN ARTERIAL PRESSURE, HEART RATE, AND ARTERIAL PULSE VOLUME OF THE LEGS DURING REST (PreLBNP) AND AT 1 MIN OF -30 TORR LBNP BEFORE AND AFTER BEDREST.

	Before Bedrest			After Bedrest		
	PreLBNP	-30 mm Hg	Percent Change	PreLBNP	-30 mm Hg	Percent Change
Mean Arterial Pressure, mm Hg	87 ± 3	85 ± 2	-1.8 ± 1.8	93 ± 2	89 ± 3	-4.5 ± 1.4
Heart Rate, bpm	55 ± 1	61 ± 2*	+11.4 ± 3.8	58 ± 3	69 ± 3*†	+18.1 ± 3.0†
Arterial Pulse Volume, ml	6.9 ± 1.4	5.4 ± 1.2*	-21.4 ± 3.4	5.9 ± 1.3†	4.6 ± 1.2*†	-20.5 ± 2.7

Values are mean ± S.E.

* $p < 0.05$ vs. corresponding PreLBNP value.

† $p < 0.05$ vs. corresponding value before bedrest.

15.5% ($p < 0.05$); and peak exercise heart rate was increased ($p < 0.05$) from 171 ± 13 bpm before bedrest to 179 ± 13 bpm after bedrest. Blood volume decreased by 14.2% ($p < 0.05$) as a result of plasma volume reduction of 581 ml (-17.0%, $p < 0.05$). Resting plasma norepinephrine levels were not significantly altered, but tolerance to LBNP in minutes was decreased by 26.9% ($p < 0.05$).

Resting heart rate was unaffected by bedrest (Table II). However, the rise in heart rate during 1 min of LBNP at -30 mm Hg was greater ($p < 0.05$) after bedrest compared to prebedrest. Bedrest had no significant effect on MAP response to 1 min of -30 mm Hg LBNP.

APV was significantly decreased by 1 min of exposure to -30 mm Hg LBNP both before and after bedrest (Table II). The level of APV (in milliliters) was significantly decreased after bedrest during rest and at 1 min of -30 mm Hg LBNP. Prior to bedrest, resting APV was 6.9 ± 1.4 ml. After bedrest, resting APV was 5.9 ± 1.3 ml (-14.8%, $p < 0.05$). At 1 min of -30 mm Hg LBNP, APV was 5.4 ± 1.2 ml before bedrest and 4.7 ± 1.2 ml (-13.3%, $p < 0.05$) following bedrest. APV was decreased ($p < 0.05$) from rest to -30 mm Hg LBNP to the same relative magnitude before and after bedrest (-21.4 ± 3.4% and -20.5 ± 2.7%, respectively).

DISCUSSION

As in previous investigations (4-6,19), 10 d of constant chronic 6° head-down bedrest reduced plasma and blood volume, peak oxygen uptake, and orthostatic tolerance. Furthermore, greater elevation in heart rate was required after bedrest to maintain similar levels of arterial pressure during mild orthostasis induced by -30 mm Hg LBNP compared to prebedrest conditions.

One mechanism that may contribute to inadequate cardiovascular responses to orthostatic stress following simulated weightlessness may be less arterial constriction due to attenuated peripheral adrenergic receptor function. Dickey *et al.* (7) observed a significant 45.7% reduction in diastolic arterial pressure associated with phenylephrine treatment after 14 d of horizontal casting in nonhuman primates. These data indicated peripheral vascular alpha-adrenergic function was reduced following hypokinesia in these animals. If alpha-adrenoceptor responsiveness was reduced with bedrest, we would have predicted less reduction in APV of the legs during LBNP after bedrest. However, we found that the magnitude of total vascular response in the legs was not altered in humans by simulated weightlessness, as indicated by the similar (21%) reduction in the percent change of leg APV during exposure to LBNP before and after bedrest.

Our results may, therefore, suggest that alpha-receptor responsiveness is not altered by simulated weightlessness.

Melada *et al.* (14) have suggested that increased vascular beta-receptor sensitivity may contribute to inadequate orthostatic stress tolerance following simulated weightlessness, since they found an increased tolerance to postbedrest tilt with beta-receptor blockade. If beta-receptor responsiveness was increased following simulated weightlessness, we would have predicted a greater APV in the legs during LBNP following bedrest. However, we found that from rest to 1 min of -30 torr LBNP, leg APV decreased by the same relative magnitude before and after bedrest. These data, therefore, suggest that beta-receptor responsiveness was not increased following bedrest. However, a limitation to our study was that we did not utilize pharmacological agents to verify specific alterations in alpha- and beta-adrenergic receptors following simulated weightlessness. Therefore, further investigation is needed to identify the contribution of specific adrenoreceptors to the leg vasculature response to orthostasis following prolonged exposure to microgravity. In any case, the net effect of 10 d of exposure to simulated weightlessness was no alteration in total vasoconstrictive response of the leg vasculature.

Another finding in our study was a reduced leg APV during rest following bedrest. One possible explanation for this finding is an increased alpha-adrenoceptor responsiveness, since a similar level of resting catecholamines observed in our study following bedrest was associated with greater vasoconstriction during rest. However, since the percent decrease in APV from rest to 1 min of -30 torr LBNP was similar before and after bedrest, we suggest that increased vascular smooth muscle responsiveness during orthostasis following simulated weightlessness was unlikely. Our hypothesis is supported by Chobanian *et al.* (4), who found that the response of mean arterial pressure to graded infusions of norepinephrine, which stimulates both alpha- and beta-receptors, was not altered by bedrest. An alternative explanation for the reduction in leg APV during rest following simulated weightlessness may be a myogenic response to a lower vascular volume associated with the observed 14% decrease in blood volume.

An implication of our study is that no apparent alteration in leg vascular smooth muscle responsiveness occurs during acute orthostatic provocation after bedrest. Therefore, our results suggest that the inability to sustain arterial pressure following reentry from spaceflight is probably not a result of ineffective reduction in peripheral vasoconstriction. The findings of Melada *et al.* (14) suggest that specific pharmacological agents (e.g. propranolol) may act as effective countermeasures against orthostatic intolerance following

bedrest. A practical application of our findings is that pharmacological agents acting on alpha- and beta-receptors of the peripheral vasculature may not provide any significant overall effect on the mechanisms controlling local peripheral resistance following spaceflight, since these responses were not affected by 10 d of bedrest.

The primary finding of our study was that there was no apparent alteration in total leg vascular smooth muscle responsiveness during acute orthostatic stress following simulated weightlessness. However, a myogenic response of vascular smooth muscle to lower vascular fluid volume associated with a plasma volume reduction may account for a higher baseline vascular constriction during rest which, in turn, may act to defend against loss in total systemic resistance following spaceflight. Finally, we suggest that pharmacological agents acting on the peripheral vasculature may not be effective countermeasures for orthostatic intolerance following prolonged exposure to actual or simulated weightlessness.

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