Evidence for increased beta-adrenoreceptor responsiveness induced by 14 days of simulated microgravity in humans

Victor A. Convertino, Jill L. Polet, Keith A. Engelke, G. Wyckliffe Hoffler, Lynda D. Lane, and C. Gunnar Blomqvist

Performing organization: Armstrong Laboratory (AFMC)
Aerospace Medicine Directorate
Clinical Sciences Division, Physiological Research Branch
2507 Kennedy Circle • Brooks AFB, TX 78235-5117

Sponsoring/monitoring agency: Life and Biomedical Sciences & Application Division
Mail Stop ULR
National Aeronautics Space Administration
Headquarters
Washington, DC 22054-0001

Supplementary notes:
Armstrong Laboratory Technical Monitor: Dr. Victor A. Convertino

Abstract:
We studied hemodynamic responses to alpha- and beta-receptor agonists in 8 healthy men (38 ± 2 yrs) before and after 14 days of 6 degree head-down tilt (HDT) to test the hypothesis that increased adrenergic responsiveness is induced by prolonged exposure to microgravity. Immediately following a 30-min baseline period, a steady-state infusion of isoproterenol (ISO) was used to assess beta 1- and beta 2-adrenergic responsiveness. ISO was infused at three graded constant rates of 0.005, 0.01 and 0.02 ug/kg/min. After heart rate and blood pressure had been allowed to return to baseline levels following ISO infusion, graded infusion of phenylephrine (PE) was used to assess responsiveness of alpha 1-vascular receptors. PE was infused at three graded constant rates of 0.25, 0.50 and 1.00 ug/kg/min. Each infusion interval for both drugs was 9 min. During the infusions, constant monitoring of beat-to-beat blood pressure and heart rate was performed and leg blood flow was measured with occlusion plethysmography at each infusion level. The slopes calculated from linear regressions between ISO and PE doses and changes in heart rate, blood pressure, and leg vascular resistance for each subject were used to represent alpha- and beta-adrenoreceptor responsiveness. Fourteen days HDT increased the slopes of heart rate (1056 ± 107 to 1553 ± 83 beats/ug/kg/min; P = 0.014) and vasodilation (-469 ± 111 to -1446 ± 309 PRU/ug/kg/min; P = 0.0224) to ISO infusion. There was no alteration in blood pressure or vascular resistance responses to PE infusion after HDT. Our results provide evidence that microgravity causes selective increases in beta 1- and beta 2-adrenergic responsiveness without affecting alpha 1-vascular responses.

Subject terms:
autonomic function; sympathetic; adrenoreceptors; heart rate; blood pressure; baroreflex; vascular resistance

Security classification:
Unclassified

Number of pages: 24
Price code: UL

20. Limitation of abstract:
Approved for public release; Distribution is unlimited.

12b. Distribution code:
Approved for public release; Distribution is unlimited.
Evidence for increased $\beta$-adrenoreceptor responsiveness induced by 14 days of simulated microgravity in humans

VICTOR A. CONVERTINO, JILL L. POLET, KEITH A. ENGELKE, G. WYCKLIFFE HOFFLER, LYNDA D. LANE, AND C. GUNNAR BLOMQVIST

Physiology Research Branch, Clinical Sciences Division, Brooks Air Force Base, Texas 78235; Biomedical Operations and Research Office, National Aeronautics and Space Administration, Kennedy Space Center, Florida 32899; Department of Physiology, University of Florida, Gainesville, Florida 32611; and University of Texas Southwestern Medical Center, Dallas, Texas 75235

Convertino, Victor A., Jill L. Polet, Keith A. Engelke, G. Wyckliffe Hoffler, Lynda D. Lane, and C. Gunnar Blomqvist. Evidence for increased $\beta$-adrenoreceptor responsiveness induced by 14 days of simulated microgravity in humans. Am. J. Physiol. 273 (Regulatory Integrative Comp. Physiol. 42): R93–R99, 1997.—We studied hemodynamic responses to $\alpha$- and $\beta$-receptor agonists in eight healthy men before and after 14 days of 6° head-down tilt (HDT) to test the hypothesis that increased adrenoreceptor responsiveness is induced by prolonged exposure to simulated microgravity. Steady-state infusions of isoproterenol (Iso) at rates of 0.005, 0.01, and 0.02 $\mu$g·kg$^{-1}$·min$^{-1}$ were used to assess $\beta_1$- and $\beta_2$-adrenoreceptor responsiveness. Infusions of phenylephrine (PE) at rates of 0.25, 0.50, and 1.00 $\mu$g·kg$^{-1}$·min$^{-1}$ were used to assess responsiveness of $\alpha_1$-vascular adrenoreceptors. Slopes calculated from linear regressions between Iso and PE doses and changes in beat-to-beat heart rate, blood pressure, and leg vascular resistance (occlusion plethysmography) for each subject were used as an index of $\alpha_1$- and $\beta$-adrenoreceptor responsiveness. HDT increased the slopes of heart rate (1,056 ± 107 to 1,553 ± 83 beats·min$^{-1}$; $P = 0.014$) and vasodilatation ($-469 ± 111$ to $-1,446 ± 309$ peripheral resistance units·$\mu$g$^{-1}$·kg$^{-1}$·min$^{-1}$; $P = 0.0224$) to Iso infusion. There was no alteration in blood pressure or vascular resistance responses to PE infusion after HDT. Our results provide evidence that simulated microgravity causes selective increases in $\beta_1$- and $\beta_2$-adrenoreceptor responsiveness without affecting $\alpha_1$-vascular adrenoreceptor responses.

METHODS

Subjects. After being informed of all procedures and risks, eight healthy, normotensive, nonsmoking men with mean (±SE) age of 38 ± 2 yr, height of 183 ± 2 cm, and weight of 81 ± 3 kg gave their written consent to serve as subjects for this investigation. All experimental procedures and protocols were approved by the Human Research Review Boards of the National Aeronautics and Space Administration (NASA)-Kennedy Space Center, NASA-Ames Research Center, and Brooks Air Force Base. Selection of subjects was based on results of a screening evaluation composed of a detailed medical history, physical examination, blood chemistry analysis, urinalysis, chest X-ray, and electrocardiogram (ECG). Subjects were made familiar with all laboratory personnel, procedures, and protocols during an orientation session conducted before the study.

General protocol. The experimental protocol comprised 4 days of ambulatory control followed by 16 days of 6° HDT and 2 days of post-HDT reambulation. During HDT, the subjects were continuously monitored by staff nurses to ensure that they remained head-down without interruption and that no physical exercise was performed by the subjects between pre- and post-HDT measurements.

During the 22-day experimental period, subjects lived 24 h/day in the Human Research Facility at NASA-Ames Research Center and followed the same controlled diet. The average daily caloric intake was 2,500–2,800 kcal (45% carbohydrate, 38% fat, 17% protein). Dietary sodium and potassium were held constant at ~120 and 60–80 meq/day.

ALTERATIONS IN autonomic function are commonly exhibited in individuals who have been exposed to microgravity environments. These include the loss of aortic, carotid, and cardiopulmonary baroreflex reserve to buffer against fluctuations in arterial and central venous blood pressures (6, 7, 9, 14). These changes in autonomic reflex control have resulted in excessive cardioacceleration and limitations in peripheral resistance responses during return to ambulation in terrestrial gravity. There is evidence that changes in central nervous system integration of afferent stimuli (12), reduced baseline vagal tone (9), and/or elevated sympathetically mediated activity (28) may contribute as underlying mechanisms.

Increased sensitivity of end-organ responses to neuroendocrine stimuli resulting from prolonged exposure to the relative inactivity of microgravity has recently been hypothesized (23). This notion is based on the inverse relationship between circulating norepinephrine (NE) and $\beta$-adrenoreceptor sensitivity. $\beta$-Adrenoreceptor activity is reduced in individuals who have elevated plasma NE as a result of regular exposure to upright posture (13) and physical exercise (4). In contrast, adrenoreceptor hypersensitivity has been reported in patients with dysautonomias in which circulating catecholamines are absent or reduced (25). Taken together, these studies and the observation that circulating plasma NE can be reduced during spaceflight (18) and in ground-based simulations of microgravity (7, 16, 23) prompt the suggestion that adrenoreceptor hypersensitivity may be a consequence of the adaptation to spaceflight.

We conducted an experiment to study the effects of prolonged exposure to a ground-based analog of microgravity (6° head-down tilt [HDT]) on various regulatory functions in human subjects (8–12). As part of that study, we tested the hypothesis that adaptation to simulated microgravity increases cardiovascular responses to adrenoreceptor agonists and that this adaptation is associated with reduced levels of circulating NE.

Evidence for increased $\beta$-adrenoreceptor responsiveness induced by 14 days of simulated microgravity in humans
respectively. Fluid intake was ad libitum; the average was 1,844 ± 17 ml/day. The photoperiod was 16 h light to 8 h dark, with lights on at 0700. The 16-day HDT period was chosen because this represents the projected minimum duration of future Extended Duration Orbiter space missions. The 6° head-down position was chosen because actual flight changes in some cardiovascular responses are closely simulated by this ground-based analog (5). Each subject underwent an adrenoreceptor response test on the third day before HDT and on day 14 of HDT. In addition, antecubital venous blood samples were drawn for determination of circulating NE and plasma volume.

Measurements of adrenoreceptor responsiveness. Each subject was moved to a quiet room on a gurney specially designed with 6° HDT, and intravenous catheters were placed in the antecubital vein of each arm while the subject was supine. All infusions were performed through the intravenous catheter placed in the left arm using an Auto-Syringe infusion pump, and administration rates were achieved by appropriate combinations of infusion rate and agonist concentrations. The catheter placed in the right arm was used to draw blood samples for analysis of plasma NE. Instrumentation was completed during a 30-min period to establish a resting baseline. Baseline measurements included plasma volume, plasma norepinephrine, heart rate (ECG), blood pressure (Finapres), and leg blood flow (LBF) (occlusion plethysmography). After baseline measurements, graded infusions of β- and α-adrenoreceptor agonists were performed with isotonic saline as a vehicle. The total volume infused was <50 ml. A recovery period of at least 30 min was allowed between the two agonist infusion protocols to allow hemodynamic measurements to return to preinfusion baseline levels. Before and during both infusion protocols, constant monitoring of beat-to-beat blood pressure and heart rate was performed. In addition, leg blood flows were measured at each infusion level. A blood sample (20 ml) for plasma NE determination was drawn at the end of the third infusion level for each drug.

β-Adrenoreceptor responsiveness. Immediately after the 30-min baseline period, infusions of isoproterenol (Iso) were used to assess the responsiveness of β- and β-adrenoreceptors. Iso was infused at three graded constant rates of 0.005, 0.01, and 0.02 μg·kg⁻¹·min⁻¹. Each infusion interval was 9 min in duration to establish steady state and allow adequate time for all measurements. The protocol and dosages of Iso [and phenylephrine (PE), see below] were adopted from those used during spaceflight experiments on NASA's Space Life Sciences (SLS)-1 and SLS-2 missions. Appropriate dosages for these adrenergic agonists were determined by laboratory experience to produce safe but significant physiological responses. An elevation of heart rate by 35 beats/min above resting baseline was the predetermined end point for test termination. However, all β-adrenoreceptor responsiveness test protocols were completed. Linear regression relationships were then constructed relating the increase in heart rate and the decrease in leg vascular resistance to the dose of Iso. The slopes describing the linear stimulus-response relationship between the dose of Iso and heart rate and leg vascular resistance provided a measure of the functional response of β- and β-adrenoreceptors, respectively.

α-Adrenoreceptor responsiveness. After heart rate and blood pressure had been allowed to return to baseline levels following Iso infusions, graded infusion of the α-adrenoreceptor agonist PE was used to assess the responsiveness of these vascular receptors. PE was infused at three graded constant rates of 0.25, 0.50, and 1.00 μg·kg⁻¹·min⁻¹. As in the case of the Iso infusion test, each infusion interval was 9 min in duration. An elevation of systolic blood pressure of 20 mmHg above or reflex reduction of heart rate 20 beats/min below resting baseline were predetermined end points for test termination. One pre-HDT and two post-HDT tests were terminated during the third stage of infusion using these criteria. The response of α-adrenoreceptors was assessed by relating the PE dose with the increment in mean arterial pressure and reduction in leg vascular resistance. The relationships between PE doses and blood pressure and leg vascular resistance were linear, and the slopes describing these relationships were used to represent an index of α-adrenoreceptor responsiveness.

Heart rate and blood pressure. Continuous heart rate was recorded using a standard three-lead ECG. A photoplethysmographic Finapres finger cuff blood pressure monitoring device was used to provide continuous beat-by-beat measurement of peripheral systolic and diastolic arterial blood pressures. Finapres recordings were verified by blood pressure measured during each stage of infusion with a sphygmomanometer. Heart rate and blood pressure responses were saved as a digital record for subsequent data analysis. Mean arterial pressure was calculated as systolic pressure plus twice diastolic divided by three.

Leg vascular resistance. LBF was measured using venous occlusion plethysmography employing a dual loop mercury-in-Silastic strain gauge placed around the left leg at the point of maximal calf circumference to determine changes in venous volume. Venous outflow from the leg was prevented by the placement of a cuff around the thigh just above the knee using an occlusion pressure of +40 mmHg. Arterial occlusion to reduce blood flow to the foot was applied by an ankle cuff inflated at a pressure of +250 mmHg. After ankle cuff inflation for 1 min, venous occlusion was initiated for 10 s, followed by its release for 10 s for six sequential occlusions. The relative change (percent) in strain gauge length over 10 s was quantified as a volume of blood per unit time, i.e., LBF. The 10-s occlusions were repeated during the final 2 min of drug infusion at each stage, and the average of the six measurements represented the LBF for that drug dose. An index of leg vascular resistance was calculated by dividing mean arterial pressure by average LBF during the final 2 min of each drug infusion and expressed as peripheral resistance units [PRU; in mmHg·l⁻¹·min⁻¹].

Plasma measurements. Plasma concentrations of NE were measured by high-performance liquid chromatography (Waters). NE was extracted by absorbing plasma samples onto alumina. After washing of the absorbed alumina with a dilute buffer solution, NE was eluted from the alumina when treated with an acidic solution. 3,4-Dihydroxybenzylamine (DHBA) was used as an internal standard, and extraction efficiency of NE and DHBA was based on the extraction of known standards. After extraction, the samples were assayed using a Waters 712 Wisp to inject the samples onto a reverse-phase C18 column. A Waters 460 electrochemical detector was used to determine the concentration of NE in the samples. The within-assay coefficient of variation (CV) was 1.4%, and between-assay CV was 3.8%.

Plasma volume was determined by a dilution technique using sterile solutions of Evans blue dye (New World Training, DeBar, FL) previously described and reported (8). Total circulating plasma NE was calculated as the product of plasma volume and plasma NE concentrations.

Statistics. Standard descriptive statistics were performed on each of the response variables of interest, with results presented as means ± SE. Standard paired t-test statistics were used to compare mean slopes of the dose-response relationships between drug infusions and heart rate, blood pressure, and vascular resistance before and after HDT and
for comparison of baseline heart rate, blood pressure, plasma NE concentrations, and total circulating NE before and after HDT. Repeated-measures analysis of variance was performed to determine differences between measurements in blood pressures and NE between pre- and post-HDT and across drug infusions. A least-significant difference (LSD) post hoc test was conducted to determine statistical differences across the drug treatments. The null hypothesis was rejected when \( P < 0.05 \).

**RESULTS**

**Baseline measurements.** Mean body weight was reduced from 81.0 ± 3.4 kg before to 79.5 ± 3.3 kg after HDT (\( t = 4.446, \) \( df = 7, \) \( P = 0.0015 \)). Baseline heart rate and leg vascular resistance were elevated by \( \text{day} \) \( 14 \) of HDT compared with pre-HDT (Fig. 1). Plasma volume was decreased by 16%, from 3,759 ± 154 ml before HDT to 3,159 ± 114 ml after HDT (5). Baseline plasma NE was reduced from 174 ± 11 pg/ml before HDT to 139 ± 6 pg/ml after HDT (\( t = 2.878, \) \( df = 7, \) \( P = 0.0237 \)). As a result of the reduction in plasma volume, total circulating NE was dramatically lowered from 655 ± 49 ng before HDT to 434 ± 15 ng after HDT (\( t = 4.685, \) \( P = 0.0022 \)).

**Adrenoreceptor responsiveness.** Fourteen days of HDT increased the average slope of the individual subject dose-response relationships between Iso and heart rate by 47%, from 1,056 ± 107 beats\( \cdot \)µg\(^{-1}\)\( \cdot \)kg\(^{-1}\)\( \cdot \)min\(^{-1}\) before HDT to 1,553 ± 83 beats\( \cdot \)µg\(^{-1}\)\( \cdot \)kg\(^{-1}\)\( \cdot \)min\(^{-1}\) on day 14 of HDT (\( t = 3.235, \) \( df = 7, \) \( P = 0.0144 \)). Figure 1 (top) represents the regressions calculated from the mean (±SE) heart rates at each Iso level before and after HDT. Similarly, the average slope of the individual subject dose-response relationships between Iso and leg vascular resistance increased by threefold from −469 ± 111 PRU\( \cdot \)µg\(^{-1}\)\( \cdot \)kg\(^{-1}\)\( \cdot \)min\(^{-1}\) before HDT to −1,146 ± 309 PRU\( \cdot \)µg\(^{-1}\)\( \cdot \)kg\(^{-1}\)\( \cdot \)min\(^{-1}\) on day 14 of HDT (\( t = 2.919, \) \( df = 7, \) \( P = 0.0224 \)). Figure 1 (bottom) represents the regressions calculated from the mean (±SE) leg vascular resistances at each Iso level before and after HDT. Mean arterial pressure was unchanged during the Iso infusions and increased during PE infusions, but there were no differences in blood pressure responses to the infusions from before to after HDT (Tables 1 and 2).

The dose-response relationship between PE and leg vascular resistance shifted upward on the response axis (Fig. 2, top) with HDT, and the average dose-response relationships between PE and mean arterial pressure before and after HDT were superimposed (Fig. 2, bottom). The average pre-HDT slope calculated from the individual subject dose-response relationships between PE and leg vascular resistance (24.7 ± 5.9 PRU\( \cdot \)µg\(^{-1}\)\( \cdot \)kg\(^{-1}\)\( \cdot \)min\(^{-1}\)) was not altered (\( t = 0.370, \) \( df = 7, \) \( P = 0.7224 \)) by HDT (27.0 ± 3.4 PRU\( \cdot \)µg\(^{-1}\)).

**Table 1. Blood pressure responses at baseline and three levels of isoproterenol infusion before and after 14 days of HDT**

<table>
<thead>
<tr>
<th>Isoproterenol, µg \cdot kg(^{-1}) \cdot min(^{-1})</th>
<th>Baseline</th>
<th>0.005</th>
<th>0.010</th>
<th>0.020</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic blood pressure, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before HDT</td>
<td>125 ± 2</td>
<td>127 ± 3</td>
<td>132 ± 4</td>
<td>132 ± 3</td>
</tr>
<tr>
<td>After HDT</td>
<td>124 ± 3</td>
<td>127 ± 3</td>
<td>132 ± 3</td>
<td>134 ± 5</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before HDT</td>
<td>75 ± 1</td>
<td>70 ± 1</td>
<td>66 ± 2</td>
<td>67 ± 2</td>
</tr>
<tr>
<td>After HDT</td>
<td>74 ± 2</td>
<td>74 ± 2</td>
<td>72 ± 2</td>
<td>73 ± 3</td>
</tr>
<tr>
<td><strong>Mean arterial pressure, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before HDT</td>
<td>92 ± 1</td>
<td>89 ± 1</td>
<td>89 ± 2</td>
<td>88 ± 2</td>
</tr>
<tr>
<td>After HDT</td>
<td>91 ± 2</td>
<td>91 ± 2</td>
<td>92 ± 2</td>
<td>94 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SE; HDT, head-down tilt. Analysis of variance revealed no statistical differences.
Table 2. Blood pressure responses at baseline and three levels of phenylephrine infusion before and after 14 days of HDT

<table>
<thead>
<tr>
<th>Systolic blood pressure, mmHg</th>
<th>Phenylephrine, µg·kg⁻¹·min⁻¹</th>
<th>Baseline</th>
<th>0.25</th>
<th>0.50</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before HDT</td>
<td></td>
<td>127 ± 2</td>
<td>132 ± 3</td>
<td>134 ± 3</td>
<td>139 ± 3</td>
</tr>
<tr>
<td>After HDT</td>
<td></td>
<td>131 ± 1</td>
<td>133 ± 1</td>
<td>139 ± 3</td>
<td>143 ± 3</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td></td>
<td>77 ± 2</td>
<td>79 ± 3</td>
<td>80 ± 3</td>
<td>84 ± 3</td>
</tr>
<tr>
<td>Before HDT</td>
<td></td>
<td>77 ± 2</td>
<td>77 ± 2</td>
<td>79 ± 2</td>
<td>84 ± 2</td>
</tr>
<tr>
<td>After HDT</td>
<td></td>
<td>94 ± 2</td>
<td>97 ± 3</td>
<td>98 ± 2</td>
<td>102 ± 3</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td></td>
<td>94 ± 1</td>
<td>96 ± 2</td>
<td>99 ± 2</td>
<td>104 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE; analysis of variance revealed no statistical differences.

kg⁻¹·min⁻¹). The average slopes calculated from the individual subject dose-response relationships between PE and mean arterial pressure before (11.9 ± 3.2 mmHg·µg⁻¹·kg⁻¹·min⁻¹) and after (12.6 ± 2.3 mmHg·µg⁻¹·kg⁻¹·min⁻¹) HDT were not statistically distinguishable (t = 0.165, df = 7, P = 0.8734).

NE responses. Both plasma concentration and total circulating plasma NE during baseline rest before HDT (174 ± 11 pg/ml and 655 ± 49 ng, respectively) were greater (t = 2.878, df = 7, P = 0.0237 and t = 4.685, df = 7, P = 0.0022, respectively) than after HDT (139 ± 7 pg/ml and 434 ± 15 ng, respectively). Under all infusion conditions, both plasma concentration and total circulating plasma NE were lower [F(1,7) = 6.67, P = 0.0363] on day 14 of HDT compared with pre-HDT (Fig. 3). Compared with preinfusion baseline, plasma NE was increased by Iso infusion and decreased by PE infusion [F(2,14) = 28.15, P = 0.0001] both before and after HDT (LSD < 57 pg/ml, P < 0.05).

DISCUSSION

We measured plasma NE, heart rate, blood pressure, and peripheral vascular responses during graded infusion of cardiac and vascular adrenoceptor agonists in eight healthy men before and after 14 days of 6° HDT to test the hypothesis that adaptation to simulated microgravity leads to adrenoceptor hypersensitivity. The major finding of this study was that HDT led to substantial increases in the heart rate and vasodilatory responses to a-β-adrenergic agonist but had little effect on the vasoconstrictive response to α-adrenergic stimulation. The results of the present study also substantiated that both circulating concentrations and total content of NE were dramatically reduced during HDT. Our data may be the first to provide evidence that microgravity may cause selective increases in β₂- and β₂-adrenoceptor responsiveness in healthy humans that were associated with reduced circulating NE without affecting α₁-vascular responses.

Tachycardia is a well-documented phenomenon associated with return to the upright posture following exposure to actual or simulated microgravity. Elevation in postflight heart rate has been attributed to hypovolemia (3), elevated catecholamines (1, 6, 12, 23, 18), and increased aortic baroreceptor responsiveness (9). Our data support the notion that increased responsiveness of cardiac β₁-adrenergic receptors represents an additional mechanism that may contribute to postspace-flight tachycardia.

In addition to chronotropic effects, the alteration in cardiac adrenoceptor responsiveness was associated with frequent occurrence of junctional or nodal arrhythmias during agonist infusion in some of our subjects. This is particularly intriguing in light of observations that altered autonomic function was postulated as a
There were no junctional rhythms in any of our eight subjects during adrenergic US Skylab missions (17). Because vascular β_{2}-adrenoreceptors elicit vasoconstriction compared with vascular constriction mediated by α_{1}-adrenoreceptors, the overall effect of greater β_{2}-responsiveness in the absence of changes in α_{1}-responses could produce a lesser vasoconstrictive effect, especially under a condition of increased sympathetic discharge during standing after return to the upright posture (30). This hypothesis is supported by the observation that normal reductions in blood flow to inactive muscle and visceral tissue during exercise did not occur in rats exposed to HDT (22). The potential to limit orthostatically induced elevations in peripheral resistance could compromise the capacity of the cardiovascular system to maintain adequate arterial blood pressure and cerebral perfusion during postspaceflight standing.

The mechanism of increased β-Adrenoreceptor responsiveness observed after HDT in the present study is unclear but may be associated with lowered sympathetic discharge (23). This hypothesis is supported in the present study by the dramatic reduction in total circulating NE at day 14 of HDT in our subjects. There is evidence from other investigations that NE is reduced during exposure to actual (18) and ground-based simulation of (6, 16, 21, 23) microgravity. β-Adrenoreceptor activity is reduced in individuals who have elevated plasma NE as a result of regular exposure to upright posture (13) and physical exercise (4), but is accentuated in subjects exposed to 10 days of HDT (21) and patients with dysautonomias in which circulating catecholamines are absent or reduced (23, 25). It is therefore possible that reduction of orthostatic and physical work stresses in a microgravity environment could be responsible for chronically reduced secretion of NE during spaceflight, leading to increased responsiveness of β-adrenoreceptors and greater tachycardia and vasodilation to sympathimetic stimulation.

Elevated circulating thyroid hormone has caused increased numbers of cardiac β-adrenoreceptors in rats (31), and hyperthyroid state is associated with low levels of plasma catecholamines in humans (20). Plasma thyroxine concentration was elevated from 7.0 ± 0.3 µg/100 ml preflight to 8.7 ± 0.5 µg/100 ml postflight in the nine crewmembers who participated in NASA's three Skylab space missions (19), and serum triiodothyronine was elevated throughout 54 days of bedrest (29). Although circulating thyroid hormone that caused increased numbers of cardiac β-adrenoreceptors in an animal model was much greater (threelfold) than normal baseline levels (31) compared with 18–24% elevation observed in humans during actual or simulated exposures to microgravity, the
possibility of thyroid hormone as a contributing mechanism to increased cardiac β-adrenergic responsiveness observed following HDT should be considered for investigation.

We chose to use steady-state rather than bolus infusion of the agonists to measure important vascular resistance data that could not be obtained by a distribution-phase method. The use of steady-state infusion could influence our interpretations if HDT altered Iso or PE clearance by the liver. We are unaware of any published data that indicate that liver function is altered by HDT or spaceflight. On the other hand, if liver metabolism of the agonists is similar to that of the endogenous catecholamines, then the interpretation of the effects of HDT on adrenoreceptor function should be appropriate.

Another limitation to the use of systemic steady-state infusion in human subjects is the presence of compensatory baroreflex responses to adrenergic stimulation. This is complicated by alterations in functions of arterial and cardiopulmonary baroreflex control of heart rate and peripheral vascular resistance induced by exposure to microgravity or its ground-based analogs (6, 7, 9, 14). The chronotropic response to equal elevations in systemic arterial pressure is increased by aortic baroreceptor stimulation (9) and reduced by carotid baroreceptor stimulation (6, 7) in subjects who have been exposed to HDT. During Iso infusion in the present experiment, arterial pressures were not altered, suggesting that it is unlikely that the increased heart rate (β₁) responsiveness was influenced by altered arterial baroreflex function. It could be argued that the elevated adrenoreceptor responsiveness following HDT observed in the present study may be underestimated because circulating NE was significantly attenuated under all baseline and infusion conditions.

Peripheral vascular adrenergic responsiveness in a hypovolemic state is heavily influenced by the cardiopulmonary baroreflex control of vascular resistance. HDT decreased plasma volume and increased the vasoconstrictive response to changes in central venous pressure (7). Although not measured during the agonist infusions in the present study, Iso infusions at doses greater than those used in our investigation have failed to alter central venous pressure (26, 27). It is therefore unlikely that changes in cardiac and vascular resistance responses to carotid, aortic, or cardiopulmonary baroreceptor control could explain alterations in β₁- and β₂-responsiveness observed after HDT in the present study.

PE is known to increase both arterial and central venous pressure (9). A hypertensive stimulus to arterial and cardiopulmonary baroreceptors would be expected to reflexly induce vasodilation by sympathetic withdrawal because peripheral vascular resistance is increased following exposure to HDT during hypotensive stimulation (7). This could lead to an underestimation of the α₁-response observed in the present study. In addition, the arterial hypertension induced by PE would be expected to elicit carotid and aortic baroreceptor-mediated vasodilation. The potential impact of these arterial baroreflexes on the peripheral α₁-response is unclear because the effect of microgravity on arterial baroreceptor control of vascular resistance is unknown.

The reduction in plasma volume may also complicate the interpretation of dose-response relationships after HDT because the concentration of the adrenergic agonists might be expected to increase by 16% if the doses of drugs were not adjusted. Because the dose-response relationships are linear, it could be suggested that 16% of the β-receptor responses was accounted for by a dilution effect. Although we did not measure the concentration of Iso or PE in the plasma, we attempted to adjust for vascular volume reduction by calculating the dose of each drug by body weight, which decreased at the end of HDT in proportion to the decrease in plasma volume (8). In any event, the increase in β₁- and β₂-adrenergic responses by 47 and 208%, respectively, indicated that these changes occurred despite the possibility of a slightly higher concentration of agonists due to hypovolemia following HDT.

**Perspectives**

The heightened β-adrenergic response following HDT in the present study may provide partial explanations for a number of physiological consequences, including orthostatic hypotension and instability, that have been commonly exhibited in individuals who have been exposed to microgravity environments. Numerous factors have been identified as potential contributing mechanisms, including hypovolemia and reduced capacity of baroreflexes to buffer against changes in blood pressure. Although hypovolemia contributes to post-spaceflight tachycardia and hypotension, it is an insufficient explanation because attempts at fluid replacement have not eliminated orthostatically induced cardioacceleration (3, 28). A sharp elevation in the amounts of NE discharged on standing after exposure to microgravity (30) could produce a more tachycardic and less vasoconstrictive character in the presence of hyperresponsive adrenoreceptors. Enhanced elevation in heart rate in a setting of hypovolemia and lower vasoconstriction is a well-known stimulus for the Bezold-Jarisch reflex and vasovagal syncope. All of the subjects in the present study experienced earlier presyncopal symptoms and orthostatic hypotension after HDT (11, 12). Therefore, in addition to hypovolemia and impaired baroreflex function, our data support the previously proposed hypothesis (23) that increased responsiveness of β-adrenoreceptors can be induced by prolonged exposure to microgravity and could contribute to post-spaceflight orthostatic intolerance.

The authors thank Drs. Joan Vernikos and Charles Wade for their assistance with this project; Dee O'Hara and her staff at the National Aeronautics and Space Administration-Ames Human Research Facility; Don Doerr, Art Maples, and Sandy Reed for engineering support; Dick Triandifils and Barry Slack for their technical assistance with this project; Dee O'Hara and her staff at the National Aeronautics and Space Administration-administered under Contracts NAS10-10285, NAG 2-408, and W-181568. K. A. Engelke was supported by a Florida Space Grant Research Consortium Fellowship.
ADRENORECEPTOR ADAPTATION TO HEAD-DOWN TILT

Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the US Air Force.

Address for reprint requests: V. A. Convertino, Physiology Research Branch, Clinical Sciences Division, AL/AOCY, 2507 Kennedy Circle, Brooks AFB, TX 78232.

Received 7 November 1996; accepted in final form 13 February 1997.

REFERENCES


