Increase in epinephrine-induced responsiveness during microgravity simulated by head-down bed rest in humans

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Barbe, P., J. Galitzky, C. Thalamas, D. Langin, M. Lafontan, J. M. Senard, and M. Berlan. Increase in epinephrine-induced responsiveness during microgravity simulated by head-down bed rest in humans. J. Appl. Physiol. 87(5): 1614–1620, 1999.—The epinephrine (Epi)-induced effects on the sympathetic nervous system (SNS) and metabolic functions were studied in men before and during a decrease in SNS activity achieved through simulated microgravity. Epi was infused at 3 graded rates (0.01, 0.02, and 0.03 µg·kg⁻¹·min⁻¹ for 40 min each) before and on the fifth day of head-down bed rest (HDBR). The effects of Epi on the SNS (assessed by plasma norepinephrine levels and spectral analysis of systolic blood pressure and heart rate variability), on plasma levels of glycerol, nonesterified fatty acids (NEFA), glucose and insulin, and on energy expenditure were evaluated. HDBR decreased urinary norepinephrine excretion (28.1 ± 4.2 vs. 51.5 ± 9.1 µg/24 h) and spectral variability of systolic blood pressure in the midfrequency range (16.3 ± 1.9 vs. 24.5 ± 0.9 normalized units). Epi increased norepinephrine plasma levels (P < 0.01) and spectral variability of systolic blood pressure (P < 0.009) during, but not before, HDBR. No modification of Epi-induced changes in heart rate and systolic and diastolic blood pressures were observed during HDBR. Epi increased plasma glucose, insulin, and NEFA levels before and during HDBR. During HDBR, the Epi-induced increase in plasma glycerol and lactate levels was more pronounced than before HDBR (P < 0.005 and P < 0.001, respectively). Epi-induced energy expenditure was higher during HDBR (P < 0.02). Our data suggest that the increased effects of Epi during simulated microgravity could be related to both the increased SNS response to Epi infusion and/or to the β-adrenergic receptor sensitization of end organs, particularly in adipose tissue and skeletal muscle.

adrenergic sensitivity; norepinephrine; lipid mobilization; energy expenditure; sympatho-inhibition

The autonomic nervous system is involved in the regulation of numerous metabolic functions. Catecholamines control the membrane adenyl cyclase activity of a large number of cells through stimulatory β-adrenergic receptors (β-ARs). Changes in sympathetic nervous system (SNS) activity have commonly been associated with altered adrenergic receptor functions in target cells. Chronic reduction of catecholamine levels led to supersensitization of inotropic and chronotropic β-AR-mediated effects in rat heart (23, 38). Adrenergic supersensitivity, associated with low plasma norepinephrine (NE) levels, was also found in patients with orthostatic hypotension (33). Autonomic function is altered in subjects exposed to microgravity environments. Simulated microgravity can be achieved during maintained –6° head-down bed rest (HDBR) (7, 12, 14, 34). HDBR decreases baroreflex gain and impairs sympathetic stimulation normally observed during orthostatism, thus explaining the adverse cardiovascular effects of weightlessness. The hemodynamic consequences of the resting state on the SNS during HDBR have been established (19, 26). Because of the reduced sympathetic activity, HDBR provides an interesting model for the study of metabolic and endocrine functions regulated by the SNS. Microgravity has been suggested to induce an increased sensitivity to adrenergic stimuli of end organs controlled by the SNS (29). This hypothesis was sustained by the fact that sympathoinhibition during HDBR induces a selective increase in β-AR responsiveness in heart (5) and adipose tissue that could be related to an increase in the postreceptor steps of the β-adrenergic pathway (3). In the same way, propranolol, a β-AR antagonist, had been beneficial (although in a limited way) as a countermeasure to cardiovascular deconditioning after bed rest (32). To our knowledge, the effect of HDBR on the adaptation of β-AR-mediated effects on integrated sympathetically-related functions and on the SNS itself has never been reported. This information could be important for an understanding of not only the autonomic disturbances in astronauts observed on their return to Earth but also other conditions (fasting, calorie restriction) or diseases (pure or metabolic autonomic failures) associated with a reduction of sympathetic activity.

Our hypothesis is that simulated microgravity increases adrenergic sensitivity of various endocrine and metabolic functions and of the SNS itself through sensitization of the β-AR pathway. In the present study, we investigated the activity of the SNS in response to epinephrine (Epi) infusion during short-term (5 days) adaptation to microgravity in humans. The effects of Epi infusion on resting energy expenditure, lipid mobilization, lactate production, insulin secretion, and the cardiovascular system were also studied.

METHODS

Subjects. Eight healthy young male subjects 23–31 yr of age [mean 27.1 ± 1.7 (SE) yr], who had not been submitted to any pharmacological or nutritional protocol before the study, were recruited. All had stable weight during the previous 3
mo, and their body mass index was 22.9 ± 0.7 kg/m² (range 19.5–24.9 kg/m²). Selection of subjects was based on a screening evaluation consisting of a detailed medical history, physical examination, complete blood count, urinalysis, resting electrocardiogram and blood pressure measurements, and several blood chemistry analyses. All subjects were nonsmokers. The study was approved by the Ethical Committee of Toulouse. All subjects gave their informed consent to the experimental conditions after being given a detailed explanation. The investigations were carried out in the Center of Clinical Investigation of the Toulouse University Hospital.

Experimental protocol. During the 6-day experimental period, subjects lived 24 h/day in the Center of Clinical Investigation of the University Hospital. The subjects were submitted to similar investigations on days 1 and 7 (i.e., before and at the end of a 5-day period of -6° HDBR, respectively) after having been placed in beds propped up at the foot with blocks to achieve a -6° head-down tilt. During this period, the subjects were supervised by using a video camera to ensure that they remained in this position throughout the experiment. The mean daily caloric intake was 2,365 ± 96 kcal. Dietary sodium and potassium intake were held constant at 90 and 80 mmol/day, respectively. Water intake was ad libitum. The photoperiod was a 16:8-h light-dark period, with lights off at 11:00 PM.

The day before the beginning of HDBR, after an overnight fast, the subjects entered the room at 8:00 AM (day 1) and were maintained in the supine position during the experimental period. At 8:30 AM, an indwelling polyethylene catheter was inserted into the antecubital vein of each arm. Infusion was performed through the intravenous catheter placed in the right arm by using an Auto-Syringe infusion pump. Administration rates were achieved by an appropriate infusion rate and Epi concentration. Blood samples were withdrawn from the catheter placed in the left arm for various analyses. Resting baseline measurements were performed during the first 40 min. Respiratory exchanges were measured for 25 min (minutes 10–35), and blood samples were taken after respiratory measurements had ceased. Immediately after the 40-min baseline period, Epi with isotonic saline as vehicle was infused at three graded constant rates of 0.01, 0.02 and 0.03 μg·kg⁻¹·min⁻¹ for 40 min each. The total volume infused was <40 ml. During the baseline period and graded Epi infusion, the heart rate was continuously recorded by using a standard three-lead electrocardiogram. Systolic and diastolic blood pressures were evaluated every 10 min by using a Dinamap device. Determining appropriate dosages for Epi was the object of preliminary tests in the laboratory to produce safe but significant physiological responses. During each infused dose of Epi, respiratory measurements were made between minutes 10 and 35 of the infusion, and blood samples were then drawn. The subjects returned to normal physiological activity until the morning of day 2, which was the first day of session. Their body composition was evaluated by dual-energy X-ray absorptiometry (DEXA) during the afternoon. The HDBR session started on the morning of day 2 and lasted a total of 5 days. Urine for 24 h was collected on days 1 and 6. On the morning of day 7, the subjects performed an identical session of investigation, in the head-down position, and a DEXA was carried out during the afternoon.

Energy expenditure and body composition measurements. Oxygen consumption and carbon dioxide production were monitored by using an open-circuit, ventilated-canopy system (Deltatrac monitor MBM-100, Datex Instrumentarium, Helsinki, Finland). The equipment was calibrated with a reference gas. Energy expenditure rate was derived from indirect calorimetry (9). The intra-assay and interassay variabilities were 1.9 and 2.6%, respectively. The results are expressed as the mean of 15-min measurements at each indicated time, and the values are given in joules per minute per kilogram of lean body mass. Body composition was assessed by DEXA by using a total-body scanner (DPX software 3.6, Lunar Radiation, Madison, WI), enabling quantification of fat mass, lean body mass, and total bone mineral content (15).

Spectral analysis of systolic blood pressure and heart rate. Blood pressure and heart rate were measured by using a Finapres device (model 2300, Ohmeda, Trappes, France) whereby a cuff was placed on the second phalange of the third finger of the dominant hand. All subjects were instructed to keep the cuffed finger at the level of the heart. Recordings were taken at the end of both the basal period and each Epi infusion. Blood pressure and heart rate data were digitalized, and a series of at least 512 equidistant values, sampled at 2 Hz without artifacts, was stored in a personal computer for off-line analysis.

Spectral analysis was performed by using a fast Fourier transform algorithm (Anapres, Notocord Systems, Croissy-sur-Seine, France). The integration of the values of the spectral modulus of the consecutive bands from 0.004 to 1 Hz was used to estimate the total spectral variability of whole spectra. In the same way, the integration of the values of consecutive bands from 70 to 130 mHz, defined as the midfrequency (MF) band, was also obtained. Results are presented as absolute values or in normalized units [NU; (MF spectral modulus/total spectral modulus) × 100].

Biochemical determinations. Plasma and urinary catecholamines were assayed by high-pressure liquid chromatography by using electrochemical (amperometric) detection, as previously described (3). The detection limit was 20 pg/sample for both catecholamines, and day-to-day variability was 4% and within-run variability was 3% for both Epi and NE. Glycerol was determined in plasma by using an ultrasensitive radiometric method (3); the intra-assay and interassay variabilities were 5.0 and 9.2%, respectively. Plasma glucose was assayed with a glucose oxidase technique (Biotrol, Paris, France); the intra-assay and interassay variabilities were 1.5 and 5.1%, respectively. Nonesterified fatty acids (NEFA) were assayed with an enzymatic method (Uniaph, Dardilly, France); the intra-assay and interassay variabilities were 1.1 and 1.6%, respectively. Plasma insulin was measured by using a Bi-insulin IRMA kit from Sanofi Diagnostics Pasteur (Marne-La-Coquette, France); the intra-assay and interassay variabilities were 2.7 and 5.8%, respectively. Plasma lactate concentrations were determined by enzymatic procedures (Sigma Chemical, l’Isle d’Abeau, France); the intraassay and interassay variabilities were 2.3 and 1.5%, respectively.

Statistical analysis. All the values are given as means ± SE. A statistical comparison of the curves was performed by using two-way ANOVA for repeated measures, with HDBR period (before vs. during) and Epi and dose as factors of the analysis. Then, the effects of Epi were analyzed in each period by using one-way ANOVA with the dose of Epi infused as the factor of the analysis, followed by a Bonferroni-Dunnett post hoc test with basal values as the control. Values were considered statistically significant when P < 0.05. Statistical analyses were performed by using Statview 4.5 and SuperAnova 1.11 (Abacus Concepts, Berkeley, CA) software packages.

RESULTS

A 5-day HDBR led to a decrease in NE and noradrenaline urine excretion without any change in plasma NE or Epi concentrations (Table 1). A body weight loss
compared with corresponding values before HDBR.

Plasma norepinephrine and epinephrine concentrations and urinary catecholamine excretion before and during 5-day HDBR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before HDBR</th>
<th>During HDBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine, pg/ml</td>
<td>269 ± 50</td>
<td>258 ± 48</td>
</tr>
<tr>
<td>Epinephrine, pg/ml</td>
<td>66 ± 16</td>
<td>53 ± 12</td>
</tr>
<tr>
<td>Creatinine, mg/24 h</td>
<td>1.400 ± 0.296</td>
<td>1.421 ± 0.189</td>
</tr>
<tr>
<td>Norepinephrine, µg/24 h</td>
<td>51.5 ± 9.1</td>
<td>28.1 ± 4.2*</td>
</tr>
<tr>
<td>Epinephrine, µg/24 h</td>
<td>6.7 ± 1.7</td>
<td>5.1 ± 1.2</td>
</tr>
<tr>
<td>Normetanephrine, µg/24 h</td>
<td>329 ± 42</td>
<td>172 ± 27*</td>
</tr>
<tr>
<td>Metanephrine, µg/24 h</td>
<td>76 ± 15</td>
<td>83 ± 10</td>
</tr>
</tbody>
</table>

Values are means ± SE. HDBR, head-down bed rest. *P < 0.01 compared with corresponding values before HDBR.

was observed (73.1 ± 3.4 vs. 72.3 ± 3.5 kg, before and during 5-day HDBR, respectively, P < 0.01) that was linked to a decrease in lean body mass (58.8 ± 2 vs. 57.8 ± 2 kg, P < 0.01), whereas fat mass (11.1 ± 1.7 vs. 11.5 ± 1.6 kg) as well as total bone mineral content (3,320 ± 129 vs. 3,341 ± 100 g) were not modified. The hematocrit significantly increased (42.1 ± 0.9 vs. 45.7 ± 0.7%, P < 0.01).

No significant changes in resting heart rate or systolic or diastolic blood pressures were observed during HDBR (Table 2). Overall spectral variability of systolic blood pressure and of heart rate was not modified by HDBR. The relative energy of the MF band of the heart also remained unchanged, whereas the relative energy of the MF band of systolic blood pressure was significantly reduced during HDBR (Table 3).

Energy expenditure was not modified during HDBR (89.2 ± 2 vs. 92 ± 2 J · min⁻¹·kg of lean body mass⁻¹). Plasma glucose, glycerol, NEFA, lactate, and insulin concentrations were not different before and during 5-day HDBR (Table 4; see Fig. 2).

Effect of graded epinephrine infusion on spectral components of systolic blood pressure and heart rate variability before and during 5-day HDBR

<table>
<thead>
<tr>
<th>Basal</th>
<th>Epinephrine Infusion, µg·kg⁻¹·min⁻¹</th>
<th>p</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.01</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>Basal</td>
<td>Before 66 ± 16</td>
<td>237 ± 21*</td>
</tr>
<tr>
<td></td>
<td>During 53 ± 12</td>
<td>221 ± 29*</td>
<td>358 ± 24*</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>Basal</td>
<td>Before 59 ± 3</td>
<td>66 ± 3*</td>
</tr>
<tr>
<td></td>
<td>During 57 ± 2</td>
<td>66 ± 3*</td>
<td>71 ± 4*</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>Basal</td>
<td>Before 116 ± 3</td>
<td>121 ± 3</td>
</tr>
<tr>
<td></td>
<td>During 129 ± 5</td>
<td>140 ± 7</td>
<td>140 ± 6*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>Basal</td>
<td>Before 62 ± 2</td>
<td>61 ± 3</td>
</tr>
<tr>
<td></td>
<td>During 67 ± 4</td>
<td>71 ± 4</td>
<td>71 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE. NS, not significant. A statistical comparison of the values was first performed by using 2-way ANOVA for repeated measures, with HDBR period (before vs. during) and epinephrine dose as factors of the analysis. The time courses of the concentration-response curves assessed by the interaction term of the 2 factors showed no significant difference on heart rate (F = 0.53; P < 0.001) and systolic (F = 0.5; P < 0.62) and diastolic blood pressures (F = 2.3; P < 0.09). Subsequently, the effects of epinephrine were analyzed in each period by using 1-way ANOVA with the dose of epinephrine infused as the factor of the analysis and followed by a Bonferroni-Dunnert post hoc test, taking basal values as control. *P < 0.05 compared with preinfusion values.
Epi concentrations before and during HDBR (Table 2). Before HDBR, and regardless of the dose of infused Epi, no significant change in plasma NE was observed. During HDBR, a significant increase in plasma NE concentration was observed at the lowest Epi dose, but subsequent higher doses did not further increase plasma NE concentrations (Fig. 1).

Effect of Epi responsiveness on cardiovascular parameters and on spectral variability. Graded Epi infusion increased heart rate before and during HDBR, the effect being significant starting from the lowest dose of Epi (Table 2). A significant increase in systolic blood pressure was observed but only with the highest dose of Epi before HDBR, whereas during HDBR an increase was observed for the two highest doses. For diastolic blood pressure, no significant effect of Epi was observed before HDBR, and a significant positive effect was observed with the highest dose during HDBR. However, ANOVA with repeated measures showed no significant effect of HDBR on Epi-induced increase in heart rate and systolic and diastolic blood pressures (Table 2).

The effects of graded Epi infusion on spectral variability are depicted in Table 3. Epi infusion failed to significantly modify overall spectral variability of systolic blood pressure or of heart rate both before and after HDBR. The relative MF energy of systolic blood pressure remained unchanged during Epi infusion before HDBR but significantly increased from the lowest Epi dose during HDBR. ANOVA with repeated measures showed that the changes in MF significantly differed between the two periods (P < 0.009). With regard to heart rate, the relative MF energy was not modified by Epi infusion either before and after HDBR.

Effect of Epi responsiveness on metabolic parameters. Before HDBR, Epi stimulated lipid mobilization, as shown by the increase in plasma glycerol concentration. A significant increase in glycerol level was observed with 0.02 and 0.03 µg·kg\(^{-1}\)·min\(^{-1}\) Epi (Fig. 2A). During HDBR, the plasma glycerol level was significantly increased with the three doses of Epi. ANOVA with repeated measures showed a significant effect of HDBR on Epi-induced increase in plasma glycerol level (P < 0.005).

As expected, Epi infusion had a positive effect on energy expenditure. Before HDBR, a significant and maximal increase in metabolic rate was observed with 0.01 µg·kg\(^{-1}\)·min\(^{-1}\) Epi (Fig. 3). During HDBR, the effect of Epi was further increased with 0.02 and 0.03 µg·kg\(^{-1}\)·min\(^{-1}\). ANOVA with repeated measures showed a significant effect of HDBR on the Epi-induced increase in energy expenditure (P < 0.02).
Epi infusion significantly increased plasma insulin and NEFA concentrations (Table 4), the maximum increase being observed with the lowest dose before and during HDBR. Epi infusion induced a dose-response increase in plasma glucose concentration before and during HDBR (Table 4). ANOVA with repeated measures showed no significant effect of HDBR on Epi-induced increase in plasma glucose, NEFA, and insulin levels. Before HDBR, the highest dose of Epi infusion (0.03 µg·kg⁻¹·min⁻¹) significantly increased plasma lactate level; the increase reached a significant level with 0.02 µg·kg⁻¹·min⁻¹ Epi during HDBR, and the maximal effect was observed with the highest dose (Fig. 2B). ANOVA with repeated measures showed a significant effect of HDBR on Epi-induced increase in plasma lactate level (P < 0.01).

DISCUSSION

Previous studies have shown that HDBR promotes a sustained reduction of sympathoneural release and a lowering of NE synthesis and turnover and induces a selective increase in β-adrenergic responsiveness in heart (5) and adipose tissue (3). Furthermore, physiological abnormalities caused by weightlessness on return from space could involve a dysregulation of the SNS (31). The present study was performed to investigate the consequences of simulated microgravity on various regulatory functions and on the SNS activity in humans. To achieve this goal, Epi-induced cardiovascular, endocrine, and metabolic modifications were studied before and during a 5-day HDBR period in humans.

Our data show that infused Epi leading to concentrations in the physiological range induces an increase in plasma NE concentrations during, but not before, HDBR. This effect was associated with an increase in the midfrequency spectral variability of systolic blood pressure, which corresponds to Mayer’s waves and thus suggests an increase in SNS activity through the involvement of the high-pressure baroreflex. These modifications were associated with an increase in Epi-induced changes in plasma glycerol and lactate levels and in energy expenditure during HDBR. These results agree with previous reports from our group (3) and others (5) showing that simulated microgravity promotes an increase in end-organ β-adrenergic pathways. The present study did not assess whether the increased lipid mobilization and energy expenditure were solely the result of the sensitization of the β-adrenergic pathway or of the increase in SNS activity. However, previous data obtained from in vitro studies in fat cells and from in situ studies using a microdialysis method have shown that hypersensitization of β-adrenergic response occurs in subcutaneous adipose tissue during HDBR (3). Thus part of the increased plasma glycerol level during HDBR could be attributable to an increased β-adrenergic sensitivity in adipose tissue. When the present results obtained during HDBR are compared with other situations known to reduce SNS activity (fasting or calorie restriction), a common increase in β-AR-induced lipolysis in adipose tissue is observed. Energy restriction increases hormone-sensitive lipase expression and sensitivity of β-AR-induced lipolysis in the fat cell (35) and the lipolytic response of adipose tissue to exogenously infused (1, 16, 37) or exercise-induced release of catecholamines (17). The changes in systolic blood pressure variability are also coherent with a putative change in β-adrenergic receptivity at the vascular level. In fact, as we found in basal conditions, Epi infusion does not modify MF spectral energy of blood pressure variability in normal volunteers (36).

Through its action on skeletal muscle, Epi is known to increase energy expenditure, with a related increase in plasma lactate (2). These effects are attributable to β-AR stimulation, and Epi is much more potent than NE for muscle glycogenolysis (2). Thus the increased Epi-induced energy expenditure and plasma lactate concentrations during HDBR could also be attributable to an increased β-adrenergic responsiveness. The Epi-induced increase in plasma glucose and insulin levels was slightly more pronounced during simulated microgravity than before, but the difference was not significant (Table 4). In fact, plasma glucose and insulin levels did not only reflect β-AR stimulation because β-ARs are also involved in the stimulation of hepatic glycogenolysis (13) and in the inhibition of insulin secretion (24, 25). Even if an increase in β-adrenergic sensitivity occurred during HDBR in liver and endocrine pancreas, the data are difficult to interpret.

Simulated microgravity increases vasoconstriction and peripheral vascular resistance (5). The mechanisms putatively involved are a decrease in atrial natriuretic peptide and an increase in renin, angiotensin II, and aldosterone secretions, these modifications being observed during at least 48-h HDBR (11). Nevertheless, no concurrently significant alteration of systolic or diastolic blood pressure was observed in basal conditions (Ref. 5 and present study). From the present data, it is unclear whether vascular responses

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**Fig. 3.** Effect of incremental infusion of epinephrine (0, 0.01, 0.02, and 0.03 µg·kg⁻¹·min⁻¹) on energy expenditure before and during 5-day head-down bed rest. Values are means ± SE. RMR, resting metabolic rate; LBM, lean body mass. Statistical analysis is described in legend of Fig. 1. Epinephrine increased resting metabolic rate before and during HDBR. Time courses of concentration-response curves assessed by interaction term of 2 factors were different (F = 3.3; P < 0.02). *P < 0.05 compared with preinfusion values.
were modified by Epi infusion because, despite higher systolic and diastolic blood pressures during HDBR, ANOVA did not reveal any effect of HDBR in response to Epi infusion (Table 2). Similarly, no effect of HDBR was found on the Epi-induced increase in heart rate and in its spectral variability. With reference to the results from Convertino et al. (5), an increase in chronotropic heart response to Epi infusion was expected during HDBR. In our experimental conditions, the absence of effect of HDBR on the Epi-induced increase in heart rate could be related to a compensatory adaptation of high-pressure baroreflex to the increase in plasma NE levels.

The mechanism of the Epi-induced increase in plasma NE levels observed during HDBR in the present study is difficult to resolve. Our study does not allow discrimination between indirect effects of Epi on sympathetic activation from Epi effects on NE release through action on prejunctional receptors. Persson et al. (28) have shown that Epi infusion increased nerve impulse traffic in sympathetic nerves and promoted a discrete rise in plasma NE concentrations. During HDBR, sensitization of β-adrenergic vascular responses to Epi may lead to a stronger SNS activation through cardiopulmonary baroreceptor control. However, our results are also compatible with an increase in sensitivity of prejunctional β-AR-mediated facilitation of transmitter release. SNS activity is controlled by presynaptic α2-ARs, the stimulation of which inhibits NE release, and by presynaptic β2-AR, which mediates an opposite function (18, 21, 22). We have previously demonstrated that the β-AR responsiveness is increased in fat cells, whereas the α2-AR responsiveness is not modified during 5-day HDBR (3). These results are also in accordance with the fact that the pressure release to NE (31) or to the selective β-AR agonist phenylephrine (5) is not modified by HDBR. If a similar differential regulation on β- and α2-AR occurs in SNS nerve endings, one can propose that the Epi-increased plasma NE level reflects an increased β-AR stimulation. Convertino et al. (4, 5) found that a 14-day HDBR induced an increased β-AR responsiveness. Furthermore, the authors found that the plasma NE level was increased by isoprenaline infusion before and, to a lesser extent, during HDBR. However, in this study, HDBR lasted for 14 days, and it can be postulated that the pronounced depletion of NE in nerve ending vesicles induced by long-term microgravity impairs NE discharge from such nerve endings (31). This may also explain why Convertino et al. (4, 5) found lower basal plasma NE level during 14-day HDBR. This was not the case during a shorter period of simulated microgravity of 5 days (Ref. 31 and present study), probably indicating that nerve depletion in NE content did not occur.

The mechanism of increased β-adrenergic responsiveness could be associated with the sustained reduction of SNS activity promoted by HDBR (31). Modifications of norepinephrine release, synthesis, and turnover have been reported during HDBR (12, 27). Spectral variability of heart rate and of systolic blood pressure has been repeatedly shown to be lower during HDBR and space-flights (10). The inhibition of SNS activity is associated with a decrease in NE excretion but not with a change in plasma NE level (Table 1). The relevance of plasma catecholamine level determinations has been questioned in this kind of experiment (12, 20). The lack of change in plasma NE level after a short-term HDBR could be explained by the concurrent hypovolemia that occurs during HDBR (Ref. 27 and present study). Even corrected with the hematocrit changes, the reduction of plasma NE level during HDBR did not reach a significant level compared with values measured before HDBR (234 ± 43 and 269 ± 50 pg/ml, respectively, P < 0.3). However, a significant reduction of plasma NE level was reported after 7 (31) or 14 (5) days of simulated gravity. In the present study, determination of catecholamine levels is not leading to a straightforward interpretation, and an unaltered plasma NE level might reflect a decreased tissue clearance of NE; however, conversely, the unaltered plasma Epi levels during Epi infusion suggest there was not a generalized decrease in catecholamine clearance.

An increase in the sensitivity of end organs exposed to low adrenergic activation has been established from animal experiments and clinical observations. Chronic reduction of catecholamine levels leads to supersensitization of the inotropic and chronotropic effects of β-AR agonists in cardiac muscle in animals (23, 38). Vascular adrenergic supersensitivity and low plasma NE levels were found in dogs treated with reserpine (8) and in Parkinson’s disease patients with orthostatic hypotension (33) or with dysautonomia (30). However, it is possible that some effects of decreased sympathetic activity promoted by HDBR differ from those described after sympathetic denervation performed by surgical or chemical means.

In conclusion, this study shows that a short-term HDBR induces an increase in adrenergic responsiveness. It is an experimental model that provides useful information for an understanding of the autonomic disturbances observed in patients with autonomic failure characterized by loss of sympathetic activity and an increased response to sympathomimetic amines (6, 29). In addition, the increment of β-adrenergic responses found, even during short-term periods of simulated microgravity (and during space travel), would also explain the autonomic disturbances occurring on return to normal gravity. Indeed, clinical pharmacological interventions with adrenergic drugs acting on SNS and/or peripheral adrenergic receptors may be of major importance in the correction of these troubles.

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