The Metabolic and Hemodynamic Effects of Prolonged Bed Rest in Normal Subjects

By Aram V. Chobanian, M.D., Robert D. Lille, M.D., Ann Tercyak, M.A., and Pengwynne Blevins, M.D.

SUMMARY
The metabolic and hemodynamic effects of prolonged bed rest were studied in 6 normal subjects. Bed rest of 2-3 weeks duration produced exaggerated responses of heart rate, cardiac output, stroke volume, and peripheral vascular resistance to 70° tilt. Sympathetic nerve function and catecholamine metabolism were not impaired by bed rest. Pressor responses to infusions of norepinephrine and angiotensin and reflex vasoconstriction to a cool and warm environment were essentially unchanged during bed rest. Plasma catecholamines and urinary vanillylmandelic acid excretion were somewhat lower during bed rest than during ambulation, but the response of plasma catecholamines to 70° tilt was not diminished. The apparent turnover of norepinephrine in plasma was also similar in bed rest and control periods. Negative sodium and potassium balances and reductions in plasma volume were observed in all subjects, but plasma renin activity and aldosterone secretory rate showed no significant change. The major decreases in sodium balance and plasma volume occurred in the early bed rest period and did not correlate closely with the degree of orthostatic intolerance. The reductions in potassium balance appeared to be progressive throughout the study.

Additional Indexing Words:
Prolonged recumbency Orthostasis Hypovolavics Catecholamine metabolism

AN UNDERSTANDING of the cardiovascular changes associated with prolonged bed rest may provide useful information about the potential effects of prolonged space exploration. Previous studies have demonstrated that orthostatic intolerance as manifested by tachycardia, hypotension, or a propensity for vasodepressor reactions is a potential complication of prolonged bed rest and in water immersion.1-5 The decreases in cardiac output and stroke volume occurring in response to the upright position are exaggerated with bed rest6 and the maximal response of cardiac output and oxygen consumption to exercise is diminished.7 These adverse circulatory responses to bed rest are not well understood but have been attributed to a variety of factors including decreased plasma volume,3,4 extravascular tissue dehydration and decreased tissue pressure,6,8 decreased venous tone,9 and failure of peripheral vasoconstriction.10 Orthostatic intolerance has been observed in astronauts following prolonged periods in space and has represented a source of potential danger to them upon re-exposure to the gravitational force on earth.11,12

The present investigation was designed to examine the influence of chronic bed rest on the interrelationships between cardiovascular hemodynamics, catecholamine metabolism, vascular reactivity, renin and aldosterone activity, and electrolyte and fluid balance. The studies were performed under metabolic balance conditions in normal subjects maintained at bed rest for 2-3 weeks.

Materials and Methods
Six healthy adult male subjects participated in these investigations. They were hospitalized at the Boston University Clinical Research Center of Boston City Hospital. Dietary sodium intake was kept constant at between 117 and 128 mEq/day and dietary potassium at 60-78 mEq/day. Total caloric intake ranged from 2200-2500 calories/day. Fluid intake was unrestricted.
The subjects were allowed to ambulate fully for the first week of hospitalization while the control measurements were made. They were then confined to strict bed rest for 2-3 weeks, at the end of which the studies were repeated. Their movements were restricted to turning in bed, and they were allowed to use one pillow under their head. On occasions when tilting experiments were performed, they were transferred from their bed to the tilt table via a stretcher. Upon completion of bed rest, they resumed their activities on the metabolic ward for an additional week while recovery experiments were being performed.

Tilting experiments were conducted on at least three occasions during the control period and at four to seven day intervals during the bed rest and recovery phases. The studies were carried out in the morning in a fasting state. All subjects were maintained at quiet recumbency for at least 30 min prior to tilting and for 15 min following the procedure. They were tilted passively at 70° for 15 min utilizing a standard motorized tilt table. Blood pressure was monitored by the indirect cuff technique and heart rate by electrocardiographic tracings. Near the end of the recumbency, tilting, and recovery periods, blood (30 cc) was removed for catecholamine and renin assays from an antecubital vein utilizing an indwelling needle that had been inserted at least 30 min prior to obtaining the initial blood sample. Following each phlebotomy, physiologic saline was infused into the subjects in amounts comparable to the quantity of blood removed.

Hemodynamic measurements were made in four of the subjects during the control period and at the completion of bed rest. Brachial artery and right atrial pressures were measured utilizing Statham transducers. Cardiac output was determined prior to and after 15 min of tilting at 70° by dye dilution technique utilizing indocyanine green and a Lexington recorder. The left ventricular ejection time index was calculated as previously described.11 Vectorcardiograms were performed by the Frank method.

The blood pressure responses to graded infusions of norepinephrine (NE) and angiotensin II amide (Hypertensin) were determined during the control and bed rest periods as previously described.12 The dose of norepinephrine ranged from 5-160 ng/min/kg and of angiotensin from 0.5-16.0 ng/min/kg.

Digital skin temperatures and digital plethysmography of upper and lower extremities were measured at room temperatures of 83°C and 68°C according to the method of Robertson and Smithwick.13 Complete urine collections were made throughout hospitalization, and daily urinary excretions of Na, K, and creatinine were determined. Plasma volume was measured in the control and bed rest periods utilizing Evans Blue dye and 10 min equilibration samples. Aldosterone secretory rate was assayed by the method of Melby et al.14 Plasma renin activity (PRA) was determined by radioimmunoassay.15 Plasma catecholamines (PCA) were assayed in duplicate by a slight modification of the double isotope derivative technique of Engelman, Portnow and Loenvberg.16 The blood was collected into tubes containing sodium citrate and ascorbate. Five ml of plasma was used in each assay. Tracer doses of [7-3H] dl-norepinephrine (New England Nuclear Corp.) were added, and the samples were chromatographed on cation exchange resin columns (Bio-Rex 70, 50-100 mesh, Bio-Rad Laboratories). The catecholamines were eluted with 0.2N HCl and the eluates were lyophilized. The catechols were converted to their 14C-labeled metanephrine derivatives utilizing [methyl-14C] S-adenosyl-L-methionine (New England Nuclear Corp.) and a preparation of catechol-o-methyl transferase isolated from rat liver.17 The reaction products were chromatographed on Bio-Rex 70 (100-200 mesh), eluted with NH4OH, converted to vanillin, extracted into toluene, and assayed for 14C and 3H radioactivity in a liquid scintillation spectrometer. The recoveries ranged from 11 to 30%.

The disappearance of labeled norepinephrine from plasma was determined in two subjects during the control and bed rest periods utilizing the technique of Gitlow and associates,18 [7-3H] dl-norepinephrine, which was purified on alumina just prior to use, was infused over a 30 min period at a subpressor dose of 0.03 μg/kg body weight/min. Venous blood samples were removed through an indwelling needle over a 24 hr period. The plasma was chromatographed on alumina. The norepinephrine containing fraction was eluted with 0.2 N acetic acid and the vanillylmandelic acid-normetanephrine (VMA-NM) fraction with H2O. The column fractions were treated as described19 and the radioactivity of whole plasma and of the acetic acid and H2O eluates from the column was determined. The radioactivity of total plasma was also assayed following lyophilization of the sample.

Clinical Observations

All subjects tolerated the prolonged periods of immobilization without serious complications. They generally demonstrated increased nervousness and irritability and complained of aching in their back muscles, particularly during the first week of bed rest. Their appetites and caloric intake remained unchanged throughout the study, but body weights decreased by 0.2-2.2 kg during bed rest.

Orthostatic Tolerance

The increase in heart rate with tilting averaged 13% in the control period, 32% following three days of bed rest, 62% after one week and 80% after three weeks of recumbency. No significant differences were observed between the heart rate and blood pressure responses to tilting with repeated determinations performed during the control period. The mean blood pressure was not influenced generally by prolonged bed rest either in the recumbent position or following tilting. Vasodepressor reactions were observed in three of 18 tilting experiments performed during bed rest. One of the episodes occurred during measurement of cardiac
output and two others during routine tilt procedures. The reactions were characterized by nausea, sweating, dizziness, and pallor, and were accompanied by marked decreases in heart rate and blood pressure. No similar episodes were observed during the control or recovery phases. No petechiae or purpuric lesions were precipitated by tilting.

Hemodynamic Measurements
Bed rest did not influence appreciably cardiac index, heart rate, stroke volume, central blood volume, left ventricular ejection time index, or peripheral vascular resistance as measured in the recumbent position (fig. 1). However, following 70° tilt, the reduction in cardiac index was exaggerated (mean decrease 17% during ambulation and 39% with bed rest). Stroke volume during tilting was considerably less with bed rest (mean 24 ml) than during ambulation (mean 53 ml). The reductions in central blood volume and left ventricular ejection time index with tilting also were somewhat greater during the bed rest phase.

Peripheral vascular resistance in the supine position was not influenced by bed rest. The increase in peripheral resistance with tilting was greater at the end of bed rest (mean resistance 2820 dynes sec/cm²) than in the control period (mean resistance 1960 dynes sec/cm²).

Peripheral Responses
The responses of the blood pressure to graded doses of norepinephrine and angiotensin are illustrated in figures 2 and 3, respectively. The doses utilized were designed to produce increases in mean arterial pressure over a range of 1-30 mm Hg. In this range, the blood pressure increase had an approximately linear relationship to the dose of either NE or angiotensin. Bed rest had no significant effect on the blood pressure response to either NE or angiotensin.

The skin temperature and oscillometric responses to warming and cooling likewise were not influenced by bed rest in any of the subjects.

Figure 1
The influence of three weeks bed rest on cardiovascular hemodynamics during recumbency and following passive tilting is illustrated. The values represent the means for the four subjects studied.

Circulation, Volume XLIX, March 1974
A mass plot of the data concerning blood pressure responses to angiotensin II amide in five subjects is presented. The slopes and intercepts of the curves obtained during control and bed rest periods were calculated for each subject and compared by paired t-test. The response of blood pressure to angiotensin infusions was not significantly affected by bed rest.

Catecholamine Metabolism

The effects of posture on plasma catecholamines are illustrated in figures 4 (top) and 5. In the control period (fig. 4, top), PCA increased within two minutes of tilting, reached a plateau level by 10 minutes, and rapidly returned to normal following termination of tilting. The mean PCA in the supine position during bed rest was slightly lower than in the control or recovery stages, but the response to tilting appeared somewhat exaggerated during bed rest (fig. 5). However, these changes in PCA with bed rest were not statistically significant.

Urinary VMA excretion was somewhat lower (mean decrease 23%) in all subjects at the end of bed rest than in the control period (table 1).

The plasma decay curve of labeled norepinephrine over a 24 hour period did not appear to be influenced by bed rest (fig. 6). Plasma NE radioactivity decreased rapidly during the first hour, followed by slower rates of disappearance later. As previously reported, the rate of decay of $^3$H-NE from plasma was exponential from approximately 3-24 hours after labeled NE administration. The half-time ($T_\frac{1}{2}$) was calculated utilizing this segment of the curve. The apparent $T_\frac{1}{2}$ of plasma NE in the two subjects studied was 230 and 278 minutes respectively in the control period, and 239 and 265 minutes after three weeks of bed rest. The decay curves for total plasma radioactivity as well as VMA-NM radioactivity were also comparable during both study periods. Little labeled NE, VMA, and NM could be recovered from plasma after 18 hours even while total plasma radioactivity re-
Table 1

Influence of Bed Rest on Urinary VMA Excretion and Aldosterone Secretion

<table>
<thead>
<tr>
<th>Subject</th>
<th>VMA excretion (%) change induced by bed rest</th>
<th>Aldosterone secretory rate</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>-39</td>
<td>-21</td>
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<td>2</td>
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<td>3</td>
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<td>5</td>
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</tr>
<tr>
<td>6</td>
<td>-4</td>
<td>-10</td>
</tr>
</tbody>
</table>

remained relatively high. Our results with lyophilization of the plasma and the previous work of Gitlow et al. suggest that much of the infused \(^{3}\)H-NE may have been converted to tritiated H\(_2\)O.

Plasma Renin Activity

With tilting, plasma renin activity (PRA) increased within two minutes of tilting and achieved a peak level by 10 minutes (fig. 4, bottom). No consistent effect of bed rest on PRA was apparent either in the recumbent position or following tilting (fig. 7). In the two subjects studied during the presyncopal episode associated with a vasodepressor reaction, the response of PRA to tilting was diminished during the hypotensive phase. However, a marked increase of PRA was observed two minutes after tilting with a return toward normal by 10 minutes (table 2).

Metabolic Balance Measurements

The results of the metabolic balance studies are summarized in table 3, and a representative case is illustrated in figure 8. All subjects developed a negative sodium and potassium balance during bed rest. The largest loss of sodium occurred during the early phase of bed rest. The negative sodium balance averaged 80 mEq for the first week, an additional 40 mEq the second week and 2 mEq the third week of recumbency. The potassium balance was negative during each week of bed rest with net losses of 16, 48, and 30 mEq for the first, second,
and third weeks, respectively. Serum potassium decreased slightly during bed rest from a mean control level of 4.6 mEq/L to values of 4.4, 4.2, and 4.1 mEq/L at 1, 2, and 3 weeks, respectively, of bed rest. Total creatinine excretion and creatinine clearances were similar throughout the study except for mild increases during the first day or two of recumbency.

Aldosterone secretory rate was reduced slightly (mean decrease 14%) in the four subjects after two or three weeks of bed rest, but the differences were not statistically significant (table 1).

Plasma volume was decreased below control levels in each of the measurements made during bed rest. The reductions averaged 305 ml at the end of the first week, 261 ml the second week, and 175 ml the third week of bed rest (fig. 9).

### Table 2

**Effects of Tilting on PRA During Vasodepressor Reactions**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control</th>
<th>Tilt (pre-syncope) (ng/ml/hr)</th>
<th>Recovery (2 min)</th>
<th>Recovery (10 min)</th>
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<td>0.52</td>
<td>2.20</td>
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<tr>
<td>2</td>
<td>0.78</td>
<td>0.84</td>
<td>1.95</td>
<td>1.06</td>
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</table>

### Other Measurements

Serum calcium averaged 9.4 mg% in the control period and 9.6 mg% at the end of bed rest. No significant changes in white blood count or differential, blood hematocrit, blood urea nitrogen, blood sugar, serum creatinine, chloride, bicarbonate, uric acid, transaminase, lactic dehydrogenase, or alkaline phosphatase occurred during bed rest. The electrocardiographic tracings and vectorcardiograms also appeared uninfluenced by bed rest.

### Discussion

Marked hemodynamic changes were precipitated by prolonged bed rest. In accord with previous observations, the normally observed changes in heart rate, stroke volume and cardiac output with tilting were accentuated considerably following bed rest. These orthostatic changes could not be attributed to any abnormality in sympathetic nervous activity which appeared to remain functionally intact during bed rest. The overall responses of PCA and of peripheral vascular resis-

### Table 3

**The Effects of Bed Rest on Sodium and Potassium Balance**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Experimental period</th>
<th>Na balance (mEq)</th>
<th>K balance (mEq)</th>
<th>Mean serum Na (mEq/L)</th>
<th>Mean serum K (mEq/L)</th>
<th>Mean ClCR (L/day)</th>
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<td>-7</td>
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<td>248</td>
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*Circulation, Volume XLIX, March 1974*
BACKGROUND EFFECTS OF BED REST

Figure 8
Serial changes in daily Na and K balances, creatinine clearance, and weight in a normal subject are plotted. The daily Na and K balances were calculated from the difference between total dietary intake and total urinary excretion of electrolyte.

Resistance to tilting were, if anything, accentuated with bed rest. Peripheral reactivity as measured by pressor responses to graded infusions of norepinephrine and angiotensin was not affected by bed rest.

Figure 9
The influence of bed rest on plasma volume is illustrated. Each point represents the mean change from control values for five subjects.

Circulation, Volume XLIX, March 1974

Reductions in plasma volume during bed rest appeared to contribute in part, but not entirely, to the orthostasis following bed rest. Decrease in plasma volume was observed consistently during the first few days of bed rest, but, as noted in the current and previous studies, partial correction of the abnormality may occur with increasing periods of recumbency even while the degree of orthostatic tachycardia is actually increasing. Correction of plasma volume with the mineralocorticoid drug 9-α-fluorohydrocortisone will tend to produce a variable effect on orthostatic intolerance unless a hyperexpansion of plasma volume and a positive sodium balance are produced. In control ambulatory subjects treated with diuretic drugs, plasma volume reductions comparable to those observed with prolonged bed rest are generally insufficient to produce orthostatic intolerance. On the other hand, the prevention of the orthostatic intolerance induced by bed rest by repeated exposure to lower body negative pressure is also associated with normalization of plasma volume. Extracellular fluid volume may decrease progressively with increased duration of bed rest but there is disagreement whether the degree of depletion is greater than that which would be accounted for by plasma volume changes alone. A reduced extravascular sodium and water could result in a reduction in tissue pressure, a decreased resistance to capillary filtration, and increased venous pooling in the lower extremities with assumption of the upright position.

Any reduction in venous tone and increased venous pooling with bed rest could contribute to a decrease in orthostatic tolerance, but the experimental data on the venous system have been somewhat conflicting. With chronic bed rest, the leg volume has been reported to either increase or remain unchanged in response to tilting. Prolonged recumbency may inhibit the expected increase in venous tone in response to lower body negative pressure. Venous distensibility may not be influenced by bed rest, but a paradoxical increase in venous compliance has been reported. Increased venous pooling was observed in astronauts following the Gemini IV and Gemini V flights but was an inconsistent finding with the Apollo VII and VIII space explorations.

There is some suggestive evidence to indicate that a decrease in myocardial function per se may also be a factor in the cardiovascular changes occurring with bed rest. Saltin et al. have observed that the maximal responses of cardiac output, stroke
volume, and oxygen consumption to both supine and upright exercise are significantly reduced by prolonged bed rest.\(^7\) While the abnormalities in cardiac function could be secondary to peripheral pooling of blood and diminished venous return to the heart, the finding of abnormal exercise responses in the supine position could reflect an unexplained cardiac effect of bed rest.

A significant sodium diuresis was observed in all of our subjects with bed rest, the maximum changes occurring in the first few days. Despite the persistently negative sodium balance and the reductions in plasma volume, PRA and aldosterone secretory rate did not increase. Recent studies of Bohnn et al. similarly have shown no significant influence of chronic bed rest on aldosterone secretion.\(^2\) Reductions in serum potassium can inhibit aldosterone production,\(^2\) but it is uncertain whether the small changes in serum potassium observed in the current study would be sufficient to influence aldosterone secretion.

The renin responses to tilting remained intact throughout the bed rest period. The only exceptions to this occurred during the vasodepressor episodes when no appreciable stimulation of PRA was produced by tilting, although a marked hyperreninemia was apparent after tilting. Similar findings have been observed during vasodepressor syncope by Oparil et al.\(^2\) and could be secondary to a decrease in renovascular resistance which may occur with vasovagal syncope.\(^2\)

While orthostatic tachycardia was a consistent finding, orthostatic hypotension was not observed in the absence of vasovagal type reactions. These findings contrast with those seen in astronauts following long-term weightlessness when orthostatic hypotension and tachycardia are quite common. A number of factors could be responsible for these differences. Significant dehydration has been noted in most astronauts following space flights and could contribute to the problem.\(^2\) The bed rest state does not eliminate entirely the influence of gravity on the body, and the degree of immobilization is probably less with bed rest than with weightlessness. Tilting the subjects periodically every 4-7 days may have also influenced the degree of cardiovascular deconditioning.

The responses of PCA and PRA to tilting were rapid during both ambulation and prolonged recumbency periods. Measurable increases in both parameters were demonstrated within two minutes of passive tilt, and plateau levels were reached by 10 minutes. Because of the sensitive method requiring relatively small amounts of blood for the catecholamine assays, serial measurements were possible without influencing cardiovascular hemodynamics by the phlebotomy itself. The normal or even possibly exaggerated increases in plasma catecholamines with tilting during chronic orthostasis contrast with the reduced levels in certain patients with orthostatic hypotension observed by Hickler et al.\(^3\) and by us.\(^2\)

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