Effect of Hypotonic Expansion on Sodium, Water, and Urea Excretion in Late Pregnancy: the Influence of Posture on These Results

MARSHALL D. LINDHEIMER and PETER V. WESTON

From the Departments of Medicine and Reproductive Biology, Case Western Reserve University School of Medicine, and the Perinatal Research Center, Cleveland Metropolitan General Hospital, Cleveland, Ohio 44109

ABSTRACT Mineralocorticoid-treated, normotensive third trimester subjects positioned in lateral recumbency were studied before and during the infusion of 300 mEq of hypotonic saline. Urinary sodium excretion increased in all subjects from a mean value of 199 to 416 μEq/min. In 12 maximally hydrated subjects free water clearance (CH₂O) and urine flow (V) increased from means of 7.54 and 9.50 to 11.6 and 14.5 ml/100 ml of glomerular filtrate (GFR) Also the ratio of urea to inulin clearance (Curea/CINi111a) increased from 0.59 to 0.64. The changes in the renal handling of water and urea suggest that fractional sodium reabsorption decreased at proximal nephron sites.

The subjects then assumed a supine position, and the results were compared to those obtained during the lateral recumbent control periods. Filtered sodium decreased in 11 experiments, but in five studies it remained up to 2.6 mEq/min above control values. There was only one instance in which a significant increase in sodium excretion occurred. It was concluded that supine recumbency blunts natriuresis despite volume expansion or an increase in the filtered load of sodium.

Finally, in the 12 hydrated subjects supine recumbency reduced Cn and V from a mean of 11.6 and 14.5 to 6.2 and 8.2 ml/100 ml of GFR. In eight of these experiments urine osmolality fell or did not change. Simultaneously, Curea/CINi111a fell from 0.64 to 0.57. These data suggest that the antinatriuresis, which occurred when the volume-expanded subjects were positioned in supine recumbency, was accompanied by a decrease in the fractional reabsorption of sodium at proximal nephron sites.

INTRODUCTION

Potent factors which affect the tubular reabsorption of sodium may be important determinants of renal sodium excretion (1, 2). For instance, the natriuresis which follows volume loading of the dog is largely due to a prompt decrease in the tubular reabsorption of sodium which is independent of mineralocorticoid activity (3–6). In this same species production of experimental salt retention is accompanied by ablation of the tubular natriuretic response (7, 8). These tubular natriuretic factors may be operable in normal man and of importance in the sodium homeostasis of patients with chronic renal disease (9, 10). They have not been investigated in pregnant subjects. A protocol was therefore designed with special reference to the pertinence of the newer concepts of tubular sodium handling to pregnancy.

Changes in the renal clearance of sodium, water, and urea induced by hypotonic saline expansion were measured in mineralocorticoid-treated third trimester subjects. The women were initially positioned in lateral recumbency, but after the volume load they assumed a supine posture. Since changing from a lateral to a supine position in late pregnancy reduces the glomerular filtration rate (GFR) (11), it was possible to reduce filtered
sodium below levels measured before saline loading and then to analyze the effects of such reductions on urinary sodium excretion. Furthermore, subjects were studied while undergoing a maximal water diuresis, and during such conditions changes in per cent of urine flow or in free water generation per unit of GFR or variations in the ratio of urea to inulin clearance may be inversely related to changes in the reabsorption of filtrate in the proximal tubule (12-14). Also, maintenance of hydration was used to eliminate any effects of antidiuretic hormone on the sodium excretion of the pregnant subjects (15, 16).

These studies demonstrated that volume expansion of lateral recumbent, third trimester pregnant women resulted in increases in both filtered and excreted sodium, and that this natriuresis was accompanied by a decrement in the fractional reabsorption of proximal filtrate. On the contrary, supine recumbency was antinatriuretic despite considerable volume loading and even when the filtered sodium remained above control values. Finally, the data suggested that when expanded lateral recumbent subjects assumed a supine decubitus position there was an increment in the fractional reabsorption of sodium in the proximal tubule.

**METHODS**

15 studies were performed on normotensive women in their third trimester of pregnancy. All subjects were volunteers who gave informed consent. They were studied in the Perinatal Research Center. Their ages ranged from 18 to 28 yr of age and their parity from 0 to 5. They had no evidence of renal or cardiovascular disease. One subject (O.S.) eventually delivered twins. No attempt was made to control dietary salt before the experiment, and on entry to the hospital the subjects received unrestricted diets.

Eight of the volunteers were prehydrated with approximately 1500 ml of water 8-10 hr before the experiment, and all subjects were studied after an overnight fast. All studies were conducted early in the morning with the subject in bed. Approximately 2 hr before the experiment each subject received 10 mg of deoxycorticosterone acetate intramuscularly, then drank water (20 ml/kg of body weight) over a period of 30-45 min. She was then catheterized with an indwelling triple lumen Foley catheter and assumed a lateral recumbent position. After she received appropriate priming doses, an intravenous infusion containing sustaining amounts of inulin and p-aminohippurate (PAH) in isotonic saline was maintained at a rate of approximately 0.5 ml/min throughout the study by a constant infusion pump. As diuresis ensued it was maintained by oral supplements of water calculated to replace urinary loss.

When urine flow was stable three to six successive collections were made. Each collection was of 10-20 min duration and was terminated by washing the bladder rapidly with 100-150 ml of sterile distilled water and 50-150 ml of air.

After completion of control collections, the patient remained in the lateral recumbent position, and an infusion of 0.5 N saline was commenced. 4 liters was infused over a period of 2 hr. Collection periods were resumed at the start of the 2nd hr and continued until a total of 300 mEq of sodium had been infused. (These collections were made in 13 of the 15 studies.) In some instances in which very high urine flows were recorded during hypotonic loading, the subjects received further oral supplements of water in amounts calculated to maintain the original positive water balance.

After the infusion the subject assumed a supine position, and 15-30 min later an additional three to six collections were made. During each of these three phases of the study two to three specimens of heparinized blood were obtained, and the plasma promptly separated. All specimens were analyzed for inulin, p-aminohippuric acid, urea, sodium, potassium, chloride, and osmolality. In addition, total plasma solids were recorded on one or more blood specimens during each group of collection periods.

After the study, the obstetrical care of each patient was managed by one of the authors (P.W.). Urine cultures were obtained at subsequent prenatal visits and in the puerperium. With one exception, all subjects remained free of urinary tract infection. Patient G.W., who was recatheterized during labor for urinary retention, contracted a postpartum infection. She was successfully treated, and her urine was sterile 4 months after delivery.

Insulin was determined by the method of Roe, Epstein, and Goldstein (17). The concentrations of plasma and urine p-aminohippuric acid were measured on the AutoAnalyzer by the method of Smith and associates (18), and urea was determined by the analyzer modification of the carbamino diacetyl reaction described by Skeggs (19). Sodium and potassium were measured by a flame photometer with an internal lithium standard. Osmolality was determined by measurement of freezing point depression.

**RESULTS**

The protocols of two experiments are given in Tables I and II. The results of all 15 studies are summarized in Table III. Subjects were originally divided into two groups, those prehydrated the evening before the study and those who were not. Since no significant differences were noted between the groups, their results are considered together.

**Sodium metabolism**

**Lateral recumbency.** In 13 experiments subjects positioned in lateral recumbency were studied before and during expansion with hypotonic saline. In these studies filtered sodium averaged 17.7 mEq/min before and rose to 19.9 mEq/min during expansion. Simultaneously, urinary sodium excretion which averaged 199 µEq/min during the control collections rose to 416 µEq/min. The amplitude of this natriuresis varied considerably among

---

1 There is a theoretical objection to measuring osmolality of urines diluted by bladder washout. The error is due to the fact that the dissociation of salts like NaCl is related to their concentration. Our subjects studied during water diuresis had urines of low osmolality. Therefore, the effects of washouts on the osmotic coefficients are minimal and virtually without effect upon the results. This fact has been verified in our laboratories where the addition of equal volumes of distilled water to 17 dilute urines (range 39-139 mOsm/kg) reduced their osmolarities 50.6% (±1.2).
the volunteers, the increases in sodium excretion ranging from a modest rise of 50 µEq/min (subject G.W.) to a substantial increase of 700 µEq/min (subject P.K.). In 10 of the 13 studies urinary sodium excretion had already risen by the start of the 2nd hr, and its rate of excretion varied little during successive collection periods (cf. Table I). In the other three experiments the natriuresis continued to increase during the 2nd hr of expansion (cf Table II). In these latter studies urine flow, too, rose slowly during the collection periods. However, the increase from the first to the last collection period did not exceed 10%.

Thus, the renal response to expansion of lateral recumbent subjects was an increase in both filtered and excreted sodium. Furthermore, and of importance to the design of this protocol, is the fact that the magnitude of the volume infused was sufficient to evoke a natriuresis before the time when the subject was requested to assume a supine position.

**Supine recumbency.** 15 subjects positioned in lateral recumbency were expanded with hypotonic saline. After the saline load they changed to the supine recumbent position. In these experiments, the results obtained during supine recumbency were compared to those obtained during the lateral recumbent control periods. The filtered load averaged 18 mEq/min during control collections, and the mean value for urinary sodium excretion was 219 µEq/min. After assumption of a supine position the filtered load of sodium averaged 16.3 mEq/min, and sodium excretion averaged 179 µEq/min. Filtered sodium fell to below control values in 11 studies (range of decrement 0.3-5.8 mEq/min).

The results of all 15 experiments are shown in Fig. 1. The graph depicts the net changes in filtered and excreted sodium. Regardless of the direction of the change in filtered load, these expanded subjects did not have a significant sodium diuresis. The only exception was subject P.K. In this case a modest natriuresis occurred despite an apparent decrease in the filtered load of sodium. In this experiment, however, a very substantial sodium diuresis was in progress when the patient assumed a supine posture. With institution of this maneuver sodium excretion actually fell more than 500 µEq/min; but the fall did not totally erase the natriuresis in

### Table I

**Effects of Hypotonic Saline Infusion and Assumption of a Supine Position in Subject D. C.**

| Time (min) | AF (mL/min) | V (mL/min) | C_{inulin} (mEq/min) | C_{PAH} (mEq/min) | P_{Na} (mEq/min) | F_{Na} (mEq/min) | U_{Na}V (mL/min) | U_{K}V (mL/min) | C_{com} GFR (X 100) | C_{inulin} GFR (X 100) | C_{urea}/C_{inulin} | FF |
|-----------|-------------|------------|----------------------|-------------------|------------------|---------------- |---------------- |-------------- |----------------- |------------------ |----------------- |---------------- |----|
|          |             |            |                      |                   |                  |               |               |              |                 |                   |                 |                |----|
| -110     |             |            |                      |                   |                  |               |               |              |                 |                   |                 |                |----|
| 0        |             |            |                      |                   |                  |               |               |              |                 |                   |                 |                |----|
| 48-59    |             |            |                      |                   |                  |               |               |              |                 |                   |                 |                |----|
| 59-69    |             |            |                      |                   |                  |               |               |              |                 |                   |                 |                |----|
| 69-90    |             |            |                      |                   |                  |               |               |              |                 |                   |                 |                |----|
| 91       |             |            |                      |                   |                  |               |               |              |                 |                   |                 |                |----|
| 144-154  |             |            |                      |                   |                  |               |               |              |                 |                   |                 |                |----|
| 154-163  |             |            |                      |                   |                  |               |               |              |                 |                   |                 |                |----|
| 163-172  |             |            |                      |                   |                  |               |               |              |                 |                   |                 |                |----|
| 172-182  |             |            |                      |                   |                  |               |               |              |                 |                   |                 |                |----|
| 192      |             |            |                      |                   |                  |               |               |              |                 |                   |                 |                |----|
| 204-218  |             |            |                      |                   |                  |               |               |              |                 |                   |                 |                |----|
| 218-245  |             |            |                      |                   |                  |               |               |              |                 |                   |                 |                |----|
| 245-269  |             |            |                      |                   |                  |               |               |              |                 |                   |                 |                |----|

Abbreviations as follows: AF = apparent urine flow including washout; V = actual urine flow; C_{inulin} = clearance of inulin; C_{PAH} = the clearance of p-aminohippurate; P_{Na} = plasma sodium; F_{Na} = filtered sodium; U_{Na}V = sodium excretion; U_{K}V = potassium excretion; C_{com} GFR (X 100) = fractional osmolar clearance; C_{urea}/C_{inulin} = urea to inulin clearance ratio; FF = filtration fraction; ( ) = interpolated value.

**Sodium Excretion in Pregnancy**
TABLE II
Effects of Hypotonic Saline Infusion and Assumption of a Supine Position in Subject B. H.

<table>
<thead>
<tr>
<th>Time</th>
<th>AF</th>
<th>V</th>
<th>C_in/min</th>
<th>C_PAH</th>
<th>PNa</th>
<th>FNa</th>
<th>UNaV</th>
<th>UNaV</th>
<th>C_{GFR}</th>
<th>C_GFR</th>
<th>C_{GFR}/C_{inulin}</th>
<th>FF</th>
</tr>
</thead>
<tbody>
<tr>
<td>min</td>
<td>ml/min</td>
<td>ml/min</td>
<td>ml/min</td>
<td>ml/min</td>
<td>mEq/liter</td>
<td>mEq/min</td>
<td>mEq/min</td>
<td>ml/min</td>
<td>ml/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-105</td>
<td>Patient received 10 mg of deoxycorticosterone acetate, i.m. Then this subject, who had received 1500 ml of water at 11 p.m. the preceding evening, ingested 20 ml of water/kg of body weight and assumed a lateral recumbent position. As diuresis ensued, supplements of water equal to urine output were given orally.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Priming dose: 250 mg of inulin, 500 mg of PAH. Infusion I started: 45 mg/min of inulin: 20 mg/min of PAH in saline at 0.5 ml/min.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-93</td>
<td>22.4</td>
<td>11</td>
<td>138</td>
<td>826</td>
<td>134</td>
<td>18.5</td>
<td>118</td>
<td>126</td>
<td>2.19</td>
<td>5.77</td>
<td>0.622</td>
<td>0.166</td>
</tr>
<tr>
<td>93-108</td>
<td>19.6</td>
<td>136</td>
<td>781</td>
<td>(135)</td>
<td>18.4</td>
<td>117</td>
<td>120</td>
<td>1.98</td>
<td>5.87</td>
<td>0.606</td>
<td>0.175</td>
<td></td>
</tr>
<tr>
<td>108-122</td>
<td>22.9</td>
<td>136</td>
<td>708</td>
<td>136</td>
<td>18.5</td>
<td>137</td>
<td>102</td>
<td>2.00</td>
<td>5.86</td>
<td>0.576</td>
<td>0.195</td>
<td></td>
</tr>
<tr>
<td>123</td>
<td>0.5 N saline started at 33.5 ml/min until 4 liters has been given.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>174-194</td>
<td>33.5</td>
<td>21.4</td>
<td>142</td>
<td>890</td>
<td>135</td>
<td>19.2</td>
<td>237</td>
<td>72.5</td>
<td>2.06</td>
<td>13.1</td>
<td>0.697</td>
<td>0.169</td>
</tr>
<tr>
<td>194-204</td>
<td>31.8</td>
<td>146</td>
<td>913</td>
<td>(136)</td>
<td>19.9</td>
<td>286</td>
<td>68.5</td>
<td>2.20</td>
<td>13.3</td>
<td>0.713</td>
<td>0.160</td>
<td></td>
</tr>
<tr>
<td>204-214</td>
<td>44.9</td>
<td>146</td>
<td>873</td>
<td>137</td>
<td>20.0</td>
<td>326</td>
<td>77.2</td>
<td>2.20</td>
<td>13.3</td>
<td>0.713</td>
<td>0.167</td>
<td></td>
</tr>
<tr>
<td>219</td>
<td>Patient assumed a supine recumbent position.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>242-257</td>
<td>24.9</td>
<td>14.9</td>
<td>136</td>
<td>814</td>
<td>137</td>
<td>18.6</td>
<td>180</td>
<td>75.7</td>
<td>2.72</td>
<td>8.99</td>
<td>0.584</td>
<td>0.167</td>
</tr>
<tr>
<td>257-273</td>
<td>24.4</td>
<td>14.6</td>
<td>139</td>
<td>861</td>
<td>137</td>
<td>19.0</td>
<td>210</td>
<td>83.6</td>
<td>2.48</td>
<td>8.00</td>
<td>0.597</td>
<td>0.161</td>
</tr>
<tr>
<td>273-313</td>
<td>24.6</td>
<td>13.5</td>
<td>131</td>
<td>839</td>
<td>136</td>
<td>17.8</td>
<td>168</td>
<td>77.5</td>
<td>2.37</td>
<td>8.47</td>
<td>0.580</td>
<td>0.156</td>
</tr>
</tbody>
</table>

Abbreviations as in Table I.

---

**FIGURE 1** Summary of 15 experiments in which subjects positioned in lateral recumbency were infused with hypotonic saline and then assumed a supine posture. Each bar represents the difference between the supine and the control periods in one experiment. The white bars represent changes in filtered sodium, the black bars, changes in excreted sodium.

M. D. Lindheimer and P. V. Weston
### Table III

**Summary of Experiments**

| Group | C\textsubscript{inulin} | P\textsubscript{Na} | F\textsubscript{Na} | U\textsubscript{Na}V | U\textsubscript{K}V | FF | C\textsubscript{crea/}
|-------|------------------|-----------------|-----------------|-----------------|-----------------|-----| C\textsubscript{inulin} | V\textsubscript{GFR} | C\textsubscript{GFR} | C\textsubscript{ERG} | U\textsubscript{osm} |
|       | ml/min | mEq/liter | ml/min | mEq/ | ml/min | mEq/ | ml/min | ml/min | ml/min | ml/min | mOsm/kg |
| B. H. | Control | 137 | 135 | 18.5 | 124 | 116 | 0.178 | 0.60 | 7.95 | 2.06 | 5.83 | 72 
| 68 kg | Loading | 145 | 135 | 19.6 | 282 | 73 | 0.161 | 0.70 | 14.9 | 2.15 | 13.2 | 43 
| P 1 | Supine | 134 | 136 | 18.2 | 186 | 79 | 0.160 | 0.59 | 10.7 | 1.86 | 8.49 | 50 
| P. R. | Control | 170 | 128 | 21.8 | 108 | 45 | 0.168 | 0.51 | 6.94 | 1.38 | 5.19 | 52 
| 89 kg | Loading | 179 | 133 | 23.8 | 178 | 49 | 0.167 | 0.57 | 10.4 | 1.68 | 8.84 | 37 
| P 1 | Supine | 161 | 131 | 21.1 | 127 | 68 | 0.141 | 0.56 | 8.32 | 1.18 | 7.15 | 38 
| M. W. | Control | 138 | 134 | 18.5 | 175 | 37 | 0.260 | 0.51 | 10.7 | 0.97 | 9.78 | 25 
| 63.2 kg | Loading | 170 | 137 | 23.3 | 506 | 59 | 0.262 | 0.57 | 17.4 | 2.79 | 15.2 | 31 
| P 1 | Supine | 142 | 135 | 19.2 | 239 | 75 | 0.231 | 0.55 | 8.73 | 1.62 | 6.68 | 49 
| P. S. | Control | 105 | 136 | 14.3 | 134 | 56 | 0.219 | 0.72 | 12.3 | 1.47 | 10.8 | 33 
| 52.9 kg | Loading | 107 | 132 | 14.1 | 204 | 36 | 0.231 | 0.66 | 15.6 | 1.15 | 14.0 | 31 
| P 1 | Supine | 80 | 135 | 10.8 | 67 | 32 | 0.191 | 0.57 | 9.76 | 1.23 | 8.40 | 35 
| C. H. | Control | 145 | 136 | 19.7 | 342 | 43 | 0.325 | 0.64 | 11.9 | 2.47 | 9.42 | 61 
| 57.5 kg | Loading | 141 | 135 | 19.1 | 461 | 47 | 0.316 | 0.75 | 15.7 | 2.56 | 13.4 | 50 
| P 0 | Supine | 109 | 135 | 14.7 | 184 | 56 | 0.297 | 0.74 | 3.62 | 1.63 | 1.96 | 135 
| J. M. | Control | 115 | 133 | 15.3 | 179 | 58 | 0.263 | 0.66 | 8.67 | 2.05 | 6.57 | 64 
| 66.7 kg | Loading | 158 | 128 | 20.2 | 372 | 51 | 0.310 | 0.61 | 10.0 | 1.97 | 8.06 | 59 
| P 1 | Supine | 113 | 131 | 14.8 | 101 | 63 | 0.262 | 0.52 | 7.15 | 2.13 | 4.96 | 81 
| M. L. | Control | 70.2 | 128 | 8.99 | 221 | 54 | 0.214 | 0.63 | 10.3 | 3.25 | 7.19 | 52 
| 41 kg | Loading | 78.0 | 127 | 9.91 | 486 | 55 | 0.217 | 0.69 | 20.0 | 7.51 | 13.1 | 50 
| P 4 | Supine | 53.3 | 128 | 6.82 | 105 | 52 | 0.156 | 0.72 | 13.1 | 3.18 | 9.95 | 47 
| O. S. | Control | 160 | 135 | 21.6 | 142 | 36 | 0.241 | 0.37 | 8.44 | 1.63 | 6.74 | 88 
| 65 kg | Loading | 186 | 130 | 24.2 | 264 | 40 | 0.237 | 0.46 | 10.9 | 2.11 | 8.82 | 91 
| P 5 | Supine | 144 | 127 | 18.3 | 83 | 44 | 0.214 | 0.34 | 8.88 | 1.67 | 6.97 | 64 
| B. T. | Control | 131 | 133 | 17.4 | 134 | 106 | 0.216 | 0.67 | 7.21 | 1.97 | 5.24 | 78 
| 113 kg | Loading | 146 | 135 | 19.7 | 257 | 119 | 0.253 | 0.71 | 10.4 | 2.07 | 8.29 | 62 
| P 4 | Supine | 147 | 136 | 20.0 | 186 | 111 | 0.209 | 0.68 | 9.11 | 2.18 | 6.94 | 65 
| B. B. | Control | 104 | 134 | 13.9 | 210 | 66 | 0.282 | 0.56 | 8.63 | 2.42 | 5.85 | 78 
| 52.8 kg | Loading | 124 | 135 | 16.7 | 402 | 71 | 0.296 | 0.71 | 11.6 | 2.44 | 9.10 | 54 
| P 1 | Supine | 52 | 136 | 8.15 | 77 | 30 | 0.304 | 0.49 | 4.02 | 1.16 | 3.09 | 80 
| D. C. | Control | 135 | 136 | 18.3 | 342 | 57 | 0.215 | 0.58 | 10.7 | 2.27 | 8.75 | 59 
| 62.6 kg | Loading | 149 | 135 | 20.1 | 777 | 65 | 0.223 | 0.61 | 18.1 | 4.17 | 14.3 | 62 
| P 0 | Supine | 144 | 135 | 19.5 | 191 | 68 | 0.207 | 0.38 | 7.64 | 1.44 | 6.20 | 53 
| P. K. | Control | 137 | 133 | 18.3 | 312 | 65 | 0.207 | 0.62 | 11.3 | 2.31 | 9.08 | 59 
| 62 kg | Loading | 164 | 130 | 21.3 | 1013 | 77 | 0.221 | 0.65 | 18.7 | 5.34 | 13.3 | 79 
| P 1 | Supine | 131 | 134 | 17.5 | 445 | 82 | 0.216 | 0.59 | 7.35 | 3.15 | 3.65 | 124 
| G. W. | Control | 166 | 142 | 23.6 | 168 | 45 | 0.256 | — | — | — | — |
| 113 kg | Loading | 161 | 139 | 22.4 | 207 | 53 | 0.256 | — | — | — | — |
| P 1 | Supine | 146 | 141 | 20.6 | 151 | 59 | 0.216 | — | — | — | — |

Control = mean of three or more stable periods before hypotonic loading of lateral recumbent subject; loading = three or more stable periods during the 2nd hr of hypotonic saline loading; supine = three or more stable periods after assumption of a supine position; P = parity; U\textsubscript{osm} = urine osmolality. (Measured osmolality multiplied by the quotient of AF/V.) Other abbreviations as in Table I.

*Sodium Excretion in Pregnancy* 951
progress. Furthermore, in four subjects no natriuresis occurred despite the recording of filtered loads of sodium above their control values, and in two of these patients (H.K. and B.T.) the increase in filtered sodium was 2 and 2.6 mEq/min, respectively.

Thus, in supine recumbency no decrease in fractional tubular sodium reabsorption could be demonstrated when the filtered load was reduced. Contrarily, this position consistently blunted the natriuresis apparent in lateral recumbency, and this blunting of the natriuresis occurred even if the filtered load of sodium remained substantially above control.

**Plasma sodium.** Plasma sodium remained stable in all experiments, with two exceptions. In the experiments on J.M. and O.S. decreases of 5 and 7 mEq/liter occurred. The average plasma sodium in each group was: control, 134 mEq/liter; loading in lateral recumbency, 133 mEq/liter; and supine recumbency, 133 mEq/liter.

**Potassium excretion.** The mean values for potassium excretion were similar in each phase of the study. They are 60, 61, and 62 μEq/min during the control, loading, and supine collection periods, respectively. The values during the individual studies are recorded in Table III. There was considerable variation among the different phases of individual experiments, but no specific patterns were noted.

**Water metabolism and urea clearances**

12 studies were conducted during which maximal water diuresis was maintained throughout the experiment. In these experiments osmolar and free water clear-

<table>
<thead>
<tr>
<th>Group</th>
<th>C_{\text{min}}</th>
<th>P_{\text{Na}}</th>
<th>F_{\text{Na}}</th>
<th>U_{\text{Na}}</th>
<th>U_{\text{K}}</th>
<th>FF</th>
<th>C_{\text{ann}}/C_{\text{min}}</th>
<th>V</th>
<th>C_{\text{ann}}</th>
<th>CH_{2}O</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ml/min</td>
<td>mEq/liter</td>
<td>mEq/min</td>
<td>μEq/min</td>
<td>μEq/min</td>
<td></td>
<td>ml/min</td>
<td></td>
<td>ml/min</td>
<td>mOsm/kg</td>
</tr>
<tr>
<td>G. Z.</td>
<td>Control</td>
<td>152</td>
<td>133</td>
<td>20.2</td>
<td>359</td>
<td>70</td>
<td>0.234</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>65.5 kg</td>
<td>123</td>
<td>131</td>
<td>16.1</td>
<td>176</td>
<td>55</td>
<td>0.210</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Supine</td>
<td>125</td>
<td>132</td>
<td>16.5</td>
<td>336</td>
<td>44</td>
<td>0.203</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P 1</td>
<td>141</td>
<td>131</td>
<td>18.5</td>
<td>368</td>
<td>61</td>
<td>0.174</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. K.</td>
<td>Control</td>
<td>161</td>
<td>133</td>
<td>18.0</td>
<td>368</td>
<td>44</td>
<td>0.203</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>56.5 kg</td>
<td>141</td>
<td>131</td>
<td>18.5</td>
<td>368</td>
<td>61</td>
<td>0.174</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2** The fractional clearance of solute-free water plotted against fractional osmolar clearance (open symbols) and against fractional urine flow (closed symbols). Circles represent control measurements, squares are the results measured during expansion of subjects positioned in lateral recumbency, and triangles the results measured when the women assumed a supine posture.

**Figure 3** The effect of an intravenous infusion of hypotonic saline on the fractional free water clearance of pregnant women positioned in lateral recumbency.

952 M. D. Lindheimer and P. V. Weston
ances were measured, and the clearances of urea and inulin were compared (Table III). During these studies changes in urine flow per 100 ml of GFR (V%) were linearly related to changes in free water clearance per 100 ml of GFR (C_H2O%). This becomes apparent when free water clearance (C_H2O) is plotted as a function of osmolar clearance (C_2O) and urine flow (V) (Fig. 2). During any phase of the experiment per cent of changes in C_2O were minimal. This is borne out by the observation that the average change of C_2O during a given study was only 1.34 ml/100 ml of GFR. Therefore any change in V was accompanied by a quantitatively similar change in C_H2O.

**Water metabolism in lateral recumbency.** C_H2O/100 ml of GFR rose in every experiment when subjects were expanded while positioned in lateral recumbency (Fig. 3). Thus, there was a rise in mean C_H2O from 7.54 to 11.6 ml/100 ml of GFR. Similarly, V increased from a mean of 9.60 to 14.5 ml/100 ml of GFR.

**The effect of supine recumbency.** The change that occurred when the lateral recumbent expanded subjects assumed a supine position is illustrated in Fig. 4. C_H2O fell in every instance from a mean of 11.6 to 6.2 ml/min/100 ml of GFR. Simultaneously, V fell from 14.5 to 8.2 ml/min/100 ml of GFR. Urine osmolalities (U_2O) are recorded in Table III. Despite the fall in both C_H2O% and V%, the osmolality remained the same or decreased in 7 of the 12 experiments. In two subjects, however (P.K. and C.H.), U_2O rose to 124 and 135 mOsm/kg, respectively.

**Urea clearances.** Changes in the ratio of urea to inulin clearances (Cereum/Cinulin) are recorded in Table III. During the control periods Cereum/Cinulin averaged 0.59. During saline loading of lateral recumbent subjects this ratio increased in 10 of the 12 studies and averaged 0.64 (increment 0.03–0.15). In the supine position Cereum/Cinulin averaged 0.57. In 11 of the 12 experiments the ratio fell when the subject assumed a supine position (decrement 0.01–0.23).

**DISCUSSION**

These experiments extend observations concerning the natriuretic response to volume expansion of pregnant women (20–23), as the changes in V%, C_H2O%, and Cereum/Cinulin suggest that during hypotonic saline loading of lateral recumbent subjects, fractional sodium reabsorption decreased in the proximal nephron. This study also underscores the importance of posture as a determinant of sodium excretion in late pregnancy, for supine recumbency was antinatriuretic despite considerable volume loading. Finally, when the expanded subject changed from lying on her side to lying on her back, the data suggest that the decrement in sodium excretion was accompanied by an increase in the fractional reabsorption of proximal filtrate.

12 subjects were studied during a state of maximal hydration. Under these conditions data relative to water and urea excretion may reflect changes in the reabsorptive activities of different loci of the nephron. For instance, Ecknoyan, Suki, Rector, and Seldin have demonstrated that during maximal water diuresis increases in C_H2O% and V%, induced by hypotonic saline loading, are indicative of an increase in the reabsorption and delivery of filtrate (sodium) to the distal diluting sites (12). In our experiments expansion of lateral recumbent pregnant subjects consistently resulted in increments of both V% and C_H2O%. Also, Goldstein, Lenz, and Levitt suggest that during maximal water diuresis changes in the ratio of Cereum/Cinulin relate inversely to changes in proximal tubular reabsorption (13). This ratio increased in 10 of the 12 studies. Therefore, the increases in C_H2O% and V%, and the increments in Cereum/Cinulin suggest that during the hypotonic saline infusion of lateral decubitus subjects, there was a decrement in the reabsorption of proximal filtrate.

---

**Sodium Excretion in Pregnancy**
When the expanded subjects assumed a supine posture \( V\% \) and \( C_{\text{Na}}\% \) decreased in every experiment. In 11 of 12 studies a decrement in \( C_{\text{urea}}/C_{\text{inulin}} \) occurred. These data per se may not be used as an index of proximal reabsorptive changes, unless one can eliminate the following possibility. The postural maneuver, by eliciting the secretion of small amounts of antidiuretic hormone, or by decreasing the GFR, might have caused an increase in the back diffusion of solute-free water at distal nephron sites (24, 25). Such back diffusion, irrespective of cause, should increase the osmolality of the final urine, and \( U_{\text{osm}} \) did in fact increase in five instances. In the remaining seven experiments, however, \( U_{\text{osm}} \) decreased or did not change, and the decrements of \( C_{\text{Na}}\% \), \( V\% \), and \( C_{\text{urea}}/C_{\text{inulin}} \) in these latter studies suggest that supine recumbency increased the fractional reabsorption of proximal filtrate.

Infusion of subjects positioned in lateral recumbency led to a saline diuresis in addition to the decrement in the fractional reabsorption of proximal filtrate. Then supine recumbency dramatically ablated the natriuresis, and simultaneously the fractional reabsorption of sodium increased in the proximal part of the nephron. Such observations, however, must not be construed as evidence that there is a causal relationship between these changes in proximal tubular reabsorption and the sodium content of the final urine. Micropuncture studies, which demonstrate that large variations in proximal tubular reabsorption may occur without any quantitative changes in urinary sodium excretion, suggest that the regulation of distal tubular reabsorption may be important determinants of renal sodium homeostasis (26–28). Although in our protocol the linear relationship between \( C_{\text{Na}}\% \) and \( V\% \) indicates that during hypotonic loading most of the increment of sodium delivered to the diluting site was in fact reabsorbed, we have no other information relevant to the dynamics of distal reabsorptive mechanisms.

Auld, Lalone, and Levinsky have given hypotonic saline to maximally hydrated, nonpregnant humans both before and after mineralocorticoid-induced chronic extracellular volume expansion (9). The results in their normal subjects are similar to those in our pregnant subjects in that saline loading results in increments of both \( V\% \) and \( C_{\text{Na}}\% \). However, the response in their chronically expanded subjects was different in that hypotonic loading evoked an exaggerated natriuresis but little change in \( C_{\text{Na}}\% \), a result interpreted by others as evidence that hypervolemia inhibits sodium reabsorption in the ascending loop of Henle (12). Since gravity is associated with an increment in extracellular volume and in the production of aldosterone (29, 30), it is of note that our pregnant subjects responded to hypotonic saline infusion in a manner similar to that of normal man and different from that seen in an experimentally induced hypervolemic state.

Another aspect of this protocol concerns further characterizations of the importance of posture to sodium excretion during pregnancy. Previous studies had shown that assumption of a supine posture results in an immediate decrement in urinary sodium excretion (11, 31). Our data extend this observation by demonstrating that supine recumbency is antinatriuretic despite considerable volume loading and even when the GFR remained above lateral recumbent control values.

In a number of the experiments, supine recumbency reduced the GFR considerably below control values. When saline-loaded, mineralocorticoid-treated dogs manifested similar reductions in their filtered sodium, urinary sodium excretion remained considerably above control values, thus demonstrating the presence of tubular natriuretic factors (3–7, 32). In this study reduction of the filtered load by assumption of a supine position did not demonstrate any natriuretic factors. The maneuver blunted natriuresis even when the filtered load of sodium remained up to 2.6 mEq/min above that recorded during lateral recumbent control periods. Recently, by requesting subjects to assume a supine position during the 2 hr of hypotonic loading, we have studied two subjects in whom urinary sodium excretion decreased, although the filtered load increased more than 5 mEq/min above lateral recumbent control values.

Thus, the antinatriuresis of supine recumbency is present regardless of the direction of the change in filtered load (Fig. 1), and in those subjects whose GFR are above control values there is a net increase in the tubular reabsorption of sodium. Furthermore, it appears that this increase is not related to any change in endogenous mineralocorticoid activity, as the subjects were given large doses of deoxycorticosterone acetate.

In attempting to explain the supine antinatriuresis of late pregnancy a number of mechanisms have been suggested. The decrease in filtered sodium has been mentioned as a causal factor (33), but in this study volume expansion before changing position resulted in a number of instances in which supine recumbency was antinatriuretic despite an increased filtered load. The increase in caval pressure induced by supine recumbency has also been implicated (31, 34–36), since in man congestion of the inferior vena cava induced by an inflatable balloon consistently reduced urinary sodium excretion (37). We have no data to support or deny this sug-

---


M. D. Lindheimer and P. V. Weston
gestion. It is of interest, though, that in the dog acute constriction of the inferior vena cava does not inhibit a natriuretic response to saline loading (7), while in this study supine recumbency caused a considerable decrease in sodium excretion. Also, an increased filtration fraction has been noted in many situations in which sodium reabsorption increases (38). In one study a small increment in the filtration fraction was noted when pregnant women changed from a lateral to a supine position (31). In another study renal function tests were done with pregnant women on their backs one day and on their sides the preceding or following day, and changes in filtration fraction were equivocal (11). In our study, in which a volume load was given before the postural maneuver, the filtration fraction decreased in 13 of 15 experiments.

The mechanism of how supine recumbency causes antinatriuresis cannot be determined from these experiments, as a number of factors implicated in the renal sodium metabolism of pregnant subjects were not controlled in the present study. Humoral agents, such as progesterone, angiotensin, and estrogen may affect renal salt handling (39-42). Physical factors also must be considered. These include changes in ureteral pressure (43-45) and in uterine blood flow induced by supine recumbency. The latter is of interest since the uterine-placental circulation has been likened to an arteriovenous shunt (45-47). Also, postural changes may affect the autonomic nervous system (48-50). Future investigations will have to take factors such as these into account.

ACKNOWLEDGMENTS

We gratefully acknowledge the invaluable technical assistance of Mr. John Powers, Mrs. Joan Virag, Mrs. Urmilla Gada, and Miss Nancy Rose. We would also like to thank Doctors A. Brian Little, George J. Gabuzda, and Robert E. Eckel for their advice and suggestions.

This work was supported in part by Grant No. FR 00210 of The Perinatal Clinical Research Center of the Division of Research Facilities and Resources, and by The Kidney Foundation of Ohio, Inc.

REFERENCES


