Acute Infusion of Synthetic Angiotensin II in Patients with Essential Hypertension

Its Effect on Renal Hemodynamics and on Electrolyte and Water Excretion

By Antonio I. Vagnucci, M.D., David P. Laulee, M.D., Roger B. Hickler, M.D., and George W. Thorn, M.D.

Since the identification and synthesis of angiotensin II, several investigators have attempted to elucidate its effects on renal function in normotensive and hypertensive subjects. Two extensive studies are available in the literature. Brown and Peart investigated the effect of acute angiotensin infusion, during water diuresis in 21 hypertensive patients, six of whom fell into the category of essential hypertension. A severely restricted renal reserve was indicated by low basal insulin and para-aminohippurate clearances and by the elevation of the blood urea nitrogen (29 to 44 mg. per cent). Nijensohn studied three normal and 17 hypertensive subjects under conditions of mannitol plus pitressin load; some of his patients were on antihypertensive treatment and no preliminary control of the diet was carried out. Analysis of both groups reveals a lack of uniformity of the renal natriuretic response to the infusion of angiotensin II, notwithstanding comparable renal hemodynamic changes. It was thought that control of variables (renal disease, antihypertensive treatment, differences in sodium balance) which complicate the interpretation of the data might contribute to a better understanding of this uneven effect of the angiotensin II in patients with essential hypertension.

Methods

Nine patients were studied. All of them, with the exception of M.B., were hypertensive subjects admitted to a clinical research ward, where extensive evaluation failed to reveal a cause for the elevation of their blood pressure. Their age, sex, race, admission blood pressure, known duration of hypertension, and associated conditions are given in Table 1. Patient M.B. is a normotensive subject who had several hospitalizations for recurring bouts of edema; a few episodes of urinary tract infection are reported in her history.

Upon admission, the subjects were placed on a constant diet of 90 mEq. of sodium and 60 mEq. of potassium per day, and an interval of 5 days was allowed to achieve a state of balance. Patient R.Mc was studied twice: on a sodium diet of 90 mEq./day (R.Mc 1) and 14 mEq./day (R.Mc 2).

In fasting recumbent subjects, water diuresis was initiated by ingestion of 1,500 ml. 1 hour prior to the study and sustained by drinking volumes equivalent to the urine passed during the collection periods. An intravenous priming dose of inulin and para-aminohippurate was given, followed by a sustaining infusion of inulin and para-aminohippurate in isotonic glucose delivered by a Bowman pump at a rate of 1 ml./minute.

At least 1 hour (equilibration period) was allowed to elapse between the priming dose and the beginning of the clearance study. At the end of

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Clinical studies carried out in the Clinical Research Center of the Harvard Medical School and Peter Bent Brigham Hospital; supported by Grant 8M01-FR-31-03, National Institutes of Health, U. S. Public Health Service and by the John A. Hartford Foundation.

A preliminary report of these data was given at the Eastern Section Meetings of the Federation for Clinical Research, Baltimore, Maryland, December 12, 1962.

*C Since many hypertensive patients show a progressive decline of their blood pressure during hospitalization, the value given is that taken during the day of admission. This value is the one that most closely matches the ambulatory, outpatient readings.
three to five control clearance periods, the infusion of angiotensin II* was started. The angiotensin solution was delivered by a Harvard syringe pump through a needle inserted into the tubing of the inulin and para-aminohippurate infusate; the arrangement was such that the patients were not aware of the pressor infusion. The delivery rate of angiotensin II ranged between 0.011 and 0.021 μg./Kg./minute for most of the subjects, with the exceptions of the normotensive subject M.B., in whom the rate was 0.0065, and patient J.J., who received a subpressor dose of 0.0046 μg./Kg./minute. The angiotensin was administered over four to six clearance periods; three to five clearance periods were obtained following the termination of the angiotensin infusion. Each clearance period lasted 15 minutes. Urine was collected through an indwelling urethral catheter by means of air wash in most of the cases. In the few studies in which isotonic bladder wash was carried out, the osmolality of the urine was suitably corrected.† Special care was taken to insure a state of the patient as basal as possible. Blood pressure was measured by a sphygmomanometer several times during the equilibration period and at least three times during each clearance period.

Inulin was analyzed according to the method described by Schreiner,4 and para-aminohippurate according to Smith et al.5 Each sample was analyzed in duplicate on two consecutive days; failure of the four readings to agree within 5 per cent prompted a repeat analysis of the sample. Sodium and potassium were measured by flame photometry, on a Technicon Autoanalyzer; chloride by electrometric titration according to the procedure suggested by Cotlove et al.6 Osmolality measurements were done on a Fiske osmometer.

Since the reliability of the biological measurements in nonsteady state conditions is poor,7,8 the statistics were computed with exclusion of the first clearance period under angiotensin infusion. Mean and standard error of the mean for the control and the angiotensin infusion values as well as the significance (t test) of the difference were calculated according to classical statistical techniques.

Results

Hemodynamic Changes

Blood Pressure

The average rise of the mean blood pressure (approximated as one half of the systolic plus diastolic) was 22 per cent (range 12 to

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*1-L-asparaginyl-5-L-valyl angiotensin octapeptide (Hypertensin—Ciba).
†From the measured U_{ORM} (mOsm./Kg. H_{2}O) value, the milliosmols due to the isotonic (glucose) washing fluid were deducted, then a correction for the dilution was made and an additional correction factor thus calculated,

\[
\text{molal freezing point depression of corrected NaCl} \quad = \quad 3.72, \\
\text{molal freezing point depression of non-electrolyte}
\]

was applied on the assumption that the NaCl is the main electrolyte of the urine. The numerator of the correction factor was taken from the International Critical Tables.3 The concentrations per liter of solution were not converted into concentrations per kilogram of water.
41 per cent) in the eight subjects receiving angiotensin II infusion at a rate ranging between 0.0065 and 0.021 \(\mu g/Kg/\)minute. Only patient J.J., in whom the rate of infusion was 0.0046 \(\mu g/Kg/\)minute, did not disclose any significant deviation from the control period (table 2). Patient F.D. had a few premature ventricular beats at the peak of his blood pressure rise; otherwise no change of importance occurred in the cardiac rate and rhythm of any of the patients.

**Inulin Clearance**

With the exception of two patients (E.C., R.Mc 2), the normotensive and all the hypertensive subjects showed a decrease in inulin clearance during the infusion of angiotensin (table 2). The minimum drop was 4 per cent (J.J.), the maximum (J.H.) was 19.5 per cent. Patient E.C. showed a rise of 17 per cent above the control period; no change was observed in patient R. Mc on a low-salt diet (control glomerular filtration rate = 98.2 ml./minute) in contrast to a drop from 111.4 ml./minute down to 97.7 ml./minute (12.3 per cent) when on a sodium diet of 90 mEq./day. Most of the baseline \(C_{IN}\) values were within normal limits; only in two subjects...
**Table 2**

**Effects of Infusion of Angiotensin II on Blood Pressure, Renal Hemodynamics, and Electrolyte Excretion (Means ± Standard Error)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Angiotensin II infusion rate µg/Kg/min.</th>
<th>Blood pressure</th>
<th>CIN ml/min.</th>
<th>CPAH ml/min.</th>
<th>F.F.</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.B.</td>
<td>0.0065</td>
<td>C 110/67</td>
<td>136.0 ±2.4</td>
<td>626.6 ±21.6</td>
<td>0.218</td>
</tr>
<tr>
<td>J.H.</td>
<td>0.0125</td>
<td>A 129/82</td>
<td>124.4 ±4.5</td>
<td>356.2 ±23.6</td>
<td>0.330</td>
</tr>
<tr>
<td>F.D.</td>
<td>0.0128</td>
<td>A 162/98</td>
<td>102.0 ±3.6</td>
<td>307.6 ±14.5</td>
<td>0.336</td>
</tr>
<tr>
<td>J.L.</td>
<td>0.020</td>
<td>A 172/115</td>
<td>96.1 ±3.5</td>
<td>250.5 ±8.2</td>
<td>0.366</td>
</tr>
<tr>
<td>M.W.</td>
<td>0.0113</td>
<td>C 196/102</td>
<td>97.8 ±4.4</td>
<td>334.0 ±40.1</td>
<td>0.332</td>
</tr>
<tr>
<td>E.C.</td>
<td>0.021</td>
<td>A 222/156</td>
<td>100.0 ±2.5</td>
<td>306.0 ±9.4</td>
<td>0.326</td>
</tr>
<tr>
<td>R.Mc 1*</td>
<td>0.0128</td>
<td>C 152/108</td>
<td>107.1 ±3.4</td>
<td>529.1 ±23.1</td>
<td>0.203</td>
</tr>
<tr>
<td>R.Mc 2†</td>
<td>0.0113</td>
<td>C 160/112</td>
<td>102.9 ±5.0</td>
<td>320.4 ±15.9</td>
<td>0.304</td>
</tr>
<tr>
<td>J.J.</td>
<td>0.0046</td>
<td>A 222/138</td>
<td>98.2 ±3.6</td>
<td>308.0 ±4.6</td>
<td>0.260</td>
</tr>
<tr>
<td>F.A.</td>
<td>0.011</td>
<td>C 200/130</td>
<td>118.6 ±2.9</td>
<td>531.7 ±11.1</td>
<td>0.223</td>
</tr>
</tbody>
</table>

* On 90 mEq./day sodium diet.
† On 14 mEq./day sodium diet.

C, control; A, angiotensin II infusion; CIN, inulin clearance; CPAH, para-aminophippurate clearance; F.F., filtration fraction; UNaV, sodium excretion; UClV, chloride excretion; UKV, potassium excretion; PNa, PCl, PK, mean values of sodium, chloride, potassium in plasma; E F Na%, sodium excreted.

(E.C. and J.J.) and in R.Mc on low-salt diet were they moderately depressed below the reported normal.9

**PAH Clearance**

In all the subjects studied, a decrease of the PAH clearance occurred. The average decrease for the whole group was 32.6 per cent, with a range of 8 to 48.4 per cent (table 2). The baseline values of the CPAH were below the reported normal in the same two subjects who had depression of the CIN (E.C. and J.J.) and in patient F.D. The depression was moderate for E.C. and F.D. and more marked in J.J.

**Filtration Fraction**

The filtration fraction invariably rose, with a minimum of 9 per cent in patient J.J. and a maximum of 63 per cent in patient F.D. (table 2).

**Electrolyte, Water, and Total Solute Excretion**

**Sodium and Chloride Excretion**

Since the changes of the chloride excretion were directionally and quantitatively similar to those of sodium, the description is limited to the excretion changes of the latter. On the basis of the response to angiotensin, it seems justified to divide the hypertensive population reported in this article into two groups: group I, sodium hypoexcretors; group II, sodium hyperexcretors (figs. 1 and 2). The mean rates are listed in table 2. No change occurred in the plasma concentration of sodium and chloride in either group.

The hypertensive group I (J.H., F.D., J.L.), characterized by a decreased excretion rate during infusion of angiotensin II, behaved similarly to the normotensive subject M.B. The remaining hypertensive patients (group II) reacted to angiotensin in exactly

*Circulation, Volume XXIX, April 1964*
RENAI EFFECTS OF ANGIOTENSIN II

<table>
<thead>
<tr>
<th>$U_{Na}$</th>
<th>$P_{Na}$</th>
<th>$U_{CV}$</th>
<th>$P_{CV}$</th>
<th>$U_{K}$</th>
<th>$P_{K}$</th>
<th>$E_{F}$</th>
<th>$Na%$</th>
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<tbody>
<tr>
<td>$\mu M./min.$</td>
<td>mL/L</td>
<td>$\mu M./min.$</td>
<td></td>
<td>$\mu M./min.$</td>
<td>mL/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>166.8 ± 4.8</td>
<td>140</td>
<td>158.6 ± 10.7</td>
<td>109</td>
<td>88.6 ± 2.6</td>
<td>4.6</td>
<td>0.85</td>
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<td>33.9t ± 2.5</td>
<td>140</td>
<td>37.9t ± 0.9</td>
<td>110</td>
<td>54.5t ± 3.8</td>
<td>3.6</td>
<td>0.38</td>
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<tr>
<td>67.7 ± 3.1</td>
<td>140</td>
<td>50.2 ± 1.9</td>
<td>102</td>
<td>75.3 ± 2.8</td>
<td>4.8</td>
<td>0.48</td>
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<tr>
<td>26.3 ± 10.9</td>
<td>142</td>
<td>26.0 ± 8.5</td>
<td>102</td>
<td>53.3t ± 4.0</td>
<td>1.16</td>
<td></td>
<td></td>
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<tr>
<td>71.0 ± 4.8</td>
<td>142</td>
<td>57.1 ± 3.4</td>
<td>102</td>
<td>75.3 ± 2.8</td>
<td>4.8</td>
<td>0.48</td>
<td></td>
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<tr>
<td>21.6t ± 2.4</td>
<td>140</td>
<td>21.6t ± 2.4</td>
<td>104</td>
<td>102.5 ± 3.3</td>
<td>4.0</td>
<td>0.37</td>
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<tr>
<td>35.3t ± 6.1</td>
<td>140</td>
<td>31.9t ± 5.1</td>
<td>112</td>
<td>110.0 ± 7.0</td>
<td>3.9</td>
<td>2.00</td>
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<td>318.6 ± 16.7</td>
<td>145</td>
<td>200.0 ± 19.7</td>
<td>102</td>
<td>102.2 ± 8.0</td>
<td>1.93</td>
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<tr>
<td>280.2 ± 26.4</td>
<td>262.2 ± 28.3</td>
<td>132</td>
<td>102.2 ± 8.0</td>
<td>1.93</td>
<td></td>
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<tr>
<td>91.0 ± 4.8</td>
<td>144</td>
<td>51.5 ± 3.1</td>
<td>104</td>
<td>56.3 ± 2.2</td>
<td>4.5</td>
<td>0.71</td>
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<tr>
<td>1369.3t ± 176.1</td>
<td>1335.3 ± 184.6</td>
<td>133.0t ± 13.0</td>
<td>9.1</td>
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<tr>
<td>115.3 ± 4.8</td>
<td>138</td>
<td>159.7 ± 3.6</td>
<td>100</td>
<td>106.3 ± 6.9</td>
<td>4.4</td>
<td>0.75</td>
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</tr>
<tr>
<td>233.0t ± 8.3</td>
<td>140</td>
<td>281.6 ± 9.4</td>
<td>97</td>
<td>91.3 ± 22.6</td>
<td>1.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38.6 ± 6.0</td>
<td>140</td>
<td>46.0 ± 2.5</td>
<td>97</td>
<td>117.3 ± 4.8</td>
<td>4.4</td>
<td>0.28</td>
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<tr>
<td>204.0t ± 23.0</td>
<td>140</td>
<td>224.3t ± 23.1</td>
<td>142.3t ± 6.2</td>
<td>1.49</td>
<td></td>
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<tr>
<td>243.7 ± 47.3</td>
<td>139</td>
<td>182.7 ± 35.7</td>
<td>102</td>
<td>106.3 ± 6.9</td>
<td>4.4</td>
<td>0.75</td>
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</tr>
<tr>
<td>458.6t ± 26.8</td>
<td>374.0t ± 30.2</td>
<td>52.0 ± 2.6</td>
<td>4.65</td>
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</tr>
<tr>
<td>173.1 ± 30.1</td>
<td>145</td>
<td>143.1 ± 23.6</td>
<td>98</td>
<td>113.2 ± 4.3</td>
<td>4.2</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>333.0t ± 31.4</td>
<td>303.6t ± 26.4</td>
<td>108.7 ± 10.0</td>
<td>2.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

the opposite fashion, namely, with an increase in the sodium excretion rate. The average decrease of the sodium excretion rate $U_{Na}V$ was 32 per cent (range 15 to 43 per cent) in group I; the average $U_{Na}V$ rise in group II was 148 per cent (range 59 to 377 per cent).

Patient M.W. was unique in that she showed no significant variation of the sodium excretion rate in spite of prolongation of the infusion of angiotensin over five clearance periods. It is notable that the response in patient R.Mc 1 was qualitatively and quantitatively similar on a normal (90 mEq./day) and low (14 mEq./day) sodium intake.

**Potassium Excretion**

The general trend of the potassium excretion was to behave like the sodium and chloride (table 2, figs. 1 and 2). The only exception was patient F.A., whose potassium rate did not rise with the sodium. The magnitude of the potassium changes did not always have the same statistical significance as the sodium and the chloride. The angiotensin infusion did not modify the control potassium concentration in the plasma in any of the subjects.

**Water and Total Solute Excretion**

In table 3 the concentration parameters of six hypertensive patients and of the normotensive subject are listed. In spite of the care taken in assuring a basal condition of maximal or at least high water diuresis, steady rate control values were not achieved in three of the experiments.

Graphical illustration of the behavior of total solute excretion rate ($U_{OSM}V$), urine flow ($V_F$), osmolar clearance ($C_{OSM}$), and free-water clearance ($C_{H_2O}$) is given in figure 1 for subjects of group I and in figure 2 for group II.

In group I (sodium hypoexcretors) $U_{OSM}$ increased, $V_F$, $U_{OSM}$, $C_{OSM}$, $C_{H_2O}$ all decreased; particularly marked was the drop of $V_F$ and $C_{H_2O}$. Patient M.W., whose electrolyte excretion did not vary from control, behaved, with regard to the concentrations, like the subjects of group I.

In the hyperexcretors (group II) all these variables increased; the rise of the free-water clearance was slight and not statistically significant. Within group II, patient F.A. de-
Table 3

Water and Total Solute Excretion after Infusion of Angiotensin II (Means ± Standard Error)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Vp ml/min.</th>
<th>Uosm mOsm./Kg. H2O</th>
<th>Uosm V μOsm/min.</th>
<th>C0sm ml/min.</th>
<th>Cn o mol/min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.B. C</td>
<td>13.8 ± 0.98</td>
<td>96 ± 4</td>
<td>1326 ± 25</td>
<td>4.6 ± 0.4</td>
<td>9.2 ± 0.6</td>
</tr>
<tr>
<td>A</td>
<td>5.2 ± 0.31</td>
<td>197 ± 12</td>
<td>1015 ± 32</td>
<td>3.5 ± 0.2</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>J.H. C</td>
<td>12.7 ± 0.92</td>
<td>109 ± 13</td>
<td>1386 ± 132</td>
<td>4.8 ± 0.4</td>
<td>8.0 ± 0.7</td>
</tr>
<tr>
<td>A</td>
<td>1.3 ± 0.57</td>
<td>1223 ± 379</td>
<td>1177 ± 19</td>
<td>4.1 ± 0.1</td>
<td>-2.7 ± 0.6</td>
</tr>
<tr>
<td>F.D. C</td>
<td>12.4 ± 0.92</td>
<td>100 ± 8</td>
<td>1240 ± 72</td>
<td>4.4 ± 0.2</td>
<td>8.0 ± 0.4</td>
</tr>
<tr>
<td>A</td>
<td>4.2 ± 0.14</td>
<td>269 ± 20</td>
<td>1132 ± 88</td>
<td>4.0 ± 0.4</td>
<td>-0.23 ± 0.6</td>
</tr>
<tr>
<td>M.W. C</td>
<td>19.3 ± 1.40</td>
<td>65 ± 2</td>
<td>1252 ± 72</td>
<td>4.1 ± 0.4</td>
<td>15.2 ± 1.0</td>
</tr>
<tr>
<td>A</td>
<td>3.8 ± 0.53</td>
<td>331 ± 4</td>
<td>1083 ± 15</td>
<td>3.6 ± 0.0</td>
<td>-0.3 ± 0.0</td>
</tr>
<tr>
<td>E.C. C</td>
<td>10.7 ± 1.00</td>
<td>113 ± 8</td>
<td>922 ± 54</td>
<td>3.1 ± 0.4</td>
<td>7.5 ± 0.8</td>
</tr>
<tr>
<td>A</td>
<td>19.1 ± 1.91</td>
<td>176 ± 7</td>
<td>3381 ± 40</td>
<td>11.5 ± 1.4</td>
<td>7.6 ± 0.8</td>
</tr>
<tr>
<td>R.Mc 2</td>
<td>10.5 ± 0.70</td>
<td>81 ± 2</td>
<td>849 ± 31</td>
<td>3.0 ± 0.1</td>
<td>7.5 ± 0.3</td>
</tr>
<tr>
<td>A</td>
<td>12.9 ± 0.81</td>
<td>96 ± 3</td>
<td>1242 ± 73</td>
<td>4.4 ± 0.3</td>
<td>8.5 ± 0.3</td>
</tr>
<tr>
<td>F.A. C</td>
<td>14.7 ± 0.80</td>
<td>70 ± 10</td>
<td>983 ± 104</td>
<td>3.5 ± 0.4</td>
<td>10.8 ± 0.8</td>
</tr>
<tr>
<td>A</td>
<td>13.9 ± 2.20</td>
<td>94 ± 10</td>
<td>1248 ± 105</td>
<td>4.4 ± 0.4</td>
<td>9.5 ± 2.3</td>
</tr>
</tbody>
</table>

+ Ninety-five per cent confidence or better.

C, control; A, angiotensin II infusion; Vp, urine flow; C0sm, osmolar clearance Cn o, free-water clearance = Vp/C0sm.

Serves separate mention; the rises of U0sm, U0sm V, and C0sm were all distinct, although their significance by t test was borderline; the urine flow and Cn o both increased above the control during the second clearance period under angiotensin, but this rise was followed by return to the baseline in the third clearance period and to a further drop, in the fourth period, to a plateau below the control, which persisted throughout the four clearance periods after the end of the angiotensin infusion. This behavior is summarized by means which are below the control means and by unusually large standard errors. In summary, with the exception of U0sm, all the other concentration parameters behaved in an opposite way in the two groups, increasing in the sodium hyper-excretors, and decreasing in the sodium hypo-excretors. The U0sm rose significantly in both groups.

Recovery Periods

During the post-angiotensin clearance periods, all parameters reversed toward control values.

Discussion

Analysis of our data and of Brown and Peart’s and of Nijensohn’s reveals two main facts: patients with essential hypertension have uniformly with regard to renal hemodynamic changes; their response goes in two opposite directions, when sodium excretion changes are considered.

In reference to the renal plasma flow and filtration fraction, they do not differ qualitatively or quantitatively from the normal response either in our patient M.B. or in the normotensive subjects reported by Bock et al., Peart, Nijensohn, and Barbour et al. The elevation of the filtration fraction occurring in all normotensive and hypertensive subjects indicates that the efferent arteriolar constriction exceeds that of the afferent arteriole. In our hypertensive group, the general trend of the glomerular filtration rate, with one exception (E.C.), is to be decreased as it occurs in the normal population; more variable response with a trend toward positive correlation with the sodium excretion rate (fig. 3) is seen in Nijensohn’s data, in which infusion of mannitol and variable degrees of expansion of the extracellular fluid may have affected the renal hemodynamic response. The values of glomerular filtration rate reported by Brown and Peart are not strictly comparable, since they are derived from single short clearance periods.

The natriuretic response to angiotensin II is difficult to explain, because of the decreased...
sodium excretion rate in group I and augmented sodium excretion rate in group II. Ten of 17 idiopathic hypertensive subjects in Nijensohn’s series were hypothesis like group I; two of the six essential hypertensive patients in Brown’s paper were also hypoexcretors. Changes of glomerular filtration rate are inadequate to explain this behavior, since the tubular sodium rejectate $\frac{E}{F} \text{Na}$ decreased in group I, and increased in group II not only in our patients (table 2) but also in Nijensohn’s series, in which a more positive correlation between changes in glomerular filtration rate and changes in sodium excretion was noticed (fig. 3). In the latter series the $\frac{E}{F} \text{Na}$ diminished an average of 25.6 per cent (range 4 to 57) in the sodium hypoexcretors; it augmented a mean of 45.5 per cent (range 16 to 95) in the sodium hyperexcretors. Variations of the renal plasma flow do not appear to be responsible, since they were directionally and quantitatively quite comparable in the normotensive subjects, or in the two hypertensive groups.

Thus, it appears that the angiotensin acts upon the renal tubules. If this is so, the question arises whether this action is a direct one or is mediated through some extratubular factors. Recent evidence points to the renin-angiotensin system as the humoral mechanism responsible for the secretion of aldosterone. Carpenter et al. have shown an immediate increase of the aldosterone secretion rate, following acute infusions of angiotensin II in hypophysectomized, nephrectomized dogs; such a rise, however, occurred only after high doses of the octapeptide and not after infusion rates (0.008 to 0.075 $\mu g$/Kg./minute), more comparable to our and similar studies. It is to be noted, however, that an increase in corticosterone did occur with the smaller infusion rates. A steroid-mediated action of the angiotensin is unlikely, since it would not explain the increased rate of sodium excretion in group II and the parallel behavior of the rate of potassium excretion, which decreased in group I and increased in group II.

A direct tubular effect of the pressor polypeptide is suggested by the work of Leyssac et al.; they found a diminution of the sodium efflux rate in cortical kidney slices of rat and rabbit after adding angiotensin II. Incidentally, a natriuretic effect of renin, perhaps due to enhanced production of endogenous angiotensin, has been reported in these two species. These in vitro data may temporarily justify ruling out an effect on sodium excretion mediated through some undefined regional changes of the blood flow in the kidneys, not measurable with our present in vivo technics.

Our study on water excretion (table 3, figs. 1 and 2) lends further support to a tubular action of the angiotensin. A rise of water reabsorption during the infusion was seen in patients of group I (sodium hypoexcretors). In patients of group II, an increase of free-water clearance occurred, as reported by

![Figure 3](http://circ.ahajournals.org/)

**Figure 3**

*Relationship between sodium excretion changes and changes of glomerular filtration rate (GFR) following infusion of angiotensin II. Percentage values. A few normal subjects (open symbols) are included.*
Brown in two subjects with natriuresis. This result is to be expected, since a relationship between $C_{H_2O}$ and solute excretion has been shown.\textsuperscript{16} This increase, however, appears below what one would expect by considering the rise in osmotic load. Therefore, the overall effect of the angiotensin II seems to favor water reabsorption. Nijensohn’s data\textsuperscript{2} are not strictly comparable to ours, since they were gathered under conditions of osmotic plus antidiuretic hormone load; an increase of water economy is also seen in this study. Investigations carried out by Peart\textsuperscript{11} and del Greco\textsuperscript{19} in patients with diabetes insipidus rule out an antidiuretic hormone-mediated effect.

Abnormalities in sodium excretion are known to arise in chronic renal disease.\textsuperscript{20} Severe renal involvement, however, cannot be held responsible for the natriuresis in group II, because such is not the case of patients R.Mc and F.A.; in Nijensohn’s series,\textsuperscript{2} patients with depression of the glomerular filtration rate and renal plasma flow are either among the sodium hyperexcretors or the sodium hypoexcretors, more frequently within the latter group.

It has been suggested by Brown and Peart\textsuperscript{1} that similar hemodynamic changes would bring about natriuresis when the control diastolic arterial pressure is 120 mm Hg or higher. Analysis of our data does not allow us to concur with their opinion. As shown in figure 4, there appears to be no relationship between the control mean blood pressure and the type of the renal response. Further, the direction of the sodium excretion does not seem to be a function of the magnitude of the blood pressure rise; a natriuretic response as well as antinatriuresis in hypertensive subjects can be obtained with subpressor doses of angiotensin (fig. 4).\textsuperscript{1}

According to del Greco,\textsuperscript{21} an increase in sodium excretion would follow infusion of angiotensin II in a state of sodium retention, antinatriuresis would occur in a condition of

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**Figure 4**

Relationship between control mean arterial pressure (left panel), changes of the mean arterial pressure (right panel), and percentage changes of sodium excretion following infusion of angiotensin II.
sodium depletion. This statement is not supported by our data, since all our patients were on the same diet (sodium, 90 mEq./day; potassium, 60 mEq./day) and were in balance. Further, natriuresis occurred (patient R.Mc 2) on a low-sodium diet; this latter finding is supported also by Laragh.22

Summary

Angiotensin II (1-L-asparaginyl-5-L-valyl angiotensin octapeptide) infused intravenously in subjects with idiopathic hypertension caused depression of the renal hemodynamics in all of them. In agreement with the findings of other investigators, more than one third of the patients showed a decrease in the rate of the sodium excretion; in the remaining subjects, the pressor infusion increased the excretion of sodium.

In all the hypertensive patients, angiotensin II favored renal reabsorption of water.

From the available evidence, it appears that angiotensin II acts upon the renal tubules. The reason for the opposite effect on sodium excretion in hypertensive patients remains unexplained.

Acknowledgment

The authors gratefully acknowledge the very capable technical assistance of Miss Joyce Adshead.

References


Observation

Hippocrates in particular is represented as excelling all others upon this head. He was indebted to nature for a sound understanding, & applied himself to the schools of the philosophers for all the learning of the age. Fortune conspired with his own industry to furnish him with several uncommon opportunities of improving himself in his particular profession. He was descended from a long race of physicians, whose recieits & experience he inherited, which he enlarged with the votive tablets from the temple of Aesculapius in his native island of Cos, by travelling into many countries in quest of further experience, & by observations sent him by his disciples out of various parts of Greece. Thus qualified for making observations, he was happily for us remarkably faithful & ingenuous in reporting them. If this great man was not perfect, it was owing to the imperfection of human nature, & some disadvantages that necessarily attend(ed) the times in which he lived. It will be proper to point out some of these, lest from the high encomiums, which he has acquired, we should be inclined to ascribe more unto him than he was capable of deserving. Knowledge in nature is justly called the daughter of Time & Experience, & indeed of much longer time & experience than we are apt to imagine after the discovery has been made. It is a great while before men are capable of making any use of what passes before them unless they are put upon the observing of it.—William HEBERDEN. An Introduction to the Study of Physic. New York, Paul B. Hoeber, Inc., 1929, p. 132.
Acute Infusion of Synthetic Angiotensin II in Patients with Essential Hypertension: Its Effect on Renal Hemodynamics and on Electrolyte and Water Excretion

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Circulation. 1964;29:523-532
doi: 10.1161/01.CIR.29.4.523

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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