Effect of Angiotensin on the Renal Transport of Sodium in Essential Hypertension

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SUMMARY
The renal function, including sodium excretion rates, were studied in 27 patients with early essential hypertension, before and during angiotensin infusions. The patients had a preparatory period of salt loading for four days taking a supplement of 7 g of NaCl. Determinations were made during two 30-minute periods before the angiotensin and for two 30-minute periods afterward. Arterial blood pressure was increased in all 27 patients and renal plasma flow decreased in 25. The glomerular filtration rate changes were not statistically significant, showing some increase in 15 and a decrease in 11 patients. When the group was divided into those in which there was a decrease in sodium excretion (11 patients), and those in which there was an increase in sodium excretion (16 patients), with angiotensin infusion, a correlation with the control blood pressure was evident. The patients in whom an increase occurred had a control mean blood pressure greater than 136 mm Hg, and those exhibiting a decrease of sodium excretion, a blood pressure less than 136 mm Hg. Salt excretion did not correlate with the increment in blood pressure or renal resistance changes. The minor changes in glomerular filtration of sodium of the two groups could not explain the different excretory patterns which are attributed to an alteration of the tubular transport of sodium.

Additional Indexing Words:
Renal function Glomerular filtration

Angiotensin reduces urinary sodium excretion and glomerular filtration rate in normotensive subjects and increases sodium excretion in hypertensive patients.\(^1\)\(^2\) Although the glomerular filtration rate remains unchanged by the substance in most hypertensives, this function has been observed to rise in some and drop in others under its effect.\(^1\) This makes it difficult to determine whether or not natriuresis is due to inhibition of tubular transport of sodium. Furthermore, it has been asserted that in essential hypertension increased sodium excretion is not the result of a tubular factor inasmuch as its excretion fraction remains unchanged.\(^3\)

The purpose of this study was to investigate whether the rise in sodium excretion observed in patients with essential hypertension under the effect of angiotensin is the result of changes in glomerular filtration rate, inhibition of tubular reabsorption, or both.

Methods
A study was made of 27 patients in the early stage of essential arterial hypertension. For 4 days before the study was carried out, patients received 7 g of sodium chloride daily in their diet and a placebo.

Renal function was studied during two 30-minute periods before administration of angiotensin and in two similar intervals under the effect of angiotensin. Glomerular filtration rate, renal plasma flow, sodium excretion, and water excretion were studied in each period. Arterial blood pressure was measured three times during the control periods and under angiotensin. Mean arterial blood pressure was calculated by taking the average of these readings and was considered as the sum of the diastolic pressure and one third of the pulse pressure. Venous pressure was measured in the arm by manometer. A dose of 4 \(\mu g/\text{min}\) of angiotensin was administered in 5% glucose solution which was infused at a constant rate of 5 ml/min.
Determinations of sodium were made by the flame photometer, and glomerular filtration rate and renal plasma flow were measured by standard methods. Values were corrected for body surface of 1.73 m². The Gómez formulas were used to calculate renal resistances.

Results

The 27 patients studied fell into two groups: one group was made up of 11 patients in whom angiotensin lowered sodium excretion (table 1) and the second group consisted of 16 patients in whom this function was increased by the substance (table 2).

Mean arterial blood pressure (MAP) increased significantly \((P<0.001)\) under the effect of angiotensin in all patients studied. In the first group, the mean value of mean arterial blood pressure during the control period was 125 mm Hg which rose to 157 mm Hg. In the second group, the mean value of mean arterial blood pressure was 150 mm Hg which increased to 180 mm Hg. Glomerular filtration rate (GFR) in the first group decreased in seven patients, increased in three, and was unchanged in one. In the second group, this function decreased in four patients and increased in 12 under the effect of angiotensin. However, the statistical analysis showed that none of the changes in either group were significant \((P>0.05)\).

Renal plasma flow (RPF) diminished in all patients with the exception of one in each group (J.A. and L.S.). This change was statistically significant.

Urinary volume \((V)\) decreased in all except two patients of the first group (N.C. and J.A.) and increased in all except two patients of the second group (J.M. and A.C.). These changes were statistically significant in group 1 \((P<0.05)\) and group 2 \((P<0.01)\).

Sodium excretion \((U_{Na},V)\) decreased significantly in all patients of the first group \((P<0.01)\) and increased in all of the second group \((P<0.001)\).

Excretion fraction of sodium \((EF_{Na})\) dropped in eight patients and rose in three (S.A., N.C., and J.A.) of the first group. The decrease was statistically significant in the group as a whole \((P<0.05)\). In the second group this function increased in all patients \((P<0.001)\).

Excretion fraction of water \((EF_{H2O})\) diminished in all patients of the first group, with the exception of two (N.C. and J.A.). This decrement was statistically significant \((P<0.05)\). This function increased in all but two patients in the second group (J.M. and A.C.), and the increment was also statistically significant \((P<0.01)\).

Afferent arteriolar resistance \((R_a)\) increased in all patients with the exception of one of the first group and one of the second group (J.A. and L.S.). The increment was statistically significant in both groups.

Efferent arteriolar resistance \((R_e)\) increased in nine patients, did not change in one (S.A.), and diminished in one (J.A.) of the first group, and also increased in all patients of the second group but one (F.T.) in whom no change was observed. Statistical analysis showed the increment in both groups to be significant.

Venular resistance \((R_v)\) increased in all but two patients (J.A. and M.L.) of the first group \((P<0.05)\). In the second group this function decreased in three patients (M.M., L.S., and R.P.), was unchanged in one (S.J.), and increased in 11. These increments were statistically significant in both groups \((P<0.05)\).

Discussion

Two types of response were produced by angiotensin in the patients studied. In the group of 11 patients, it caused a drop in sodium excretion, and in the other group, of 16 patients, an increase (fig. 1).

In the group in which urinary sodium excretion decreased, glomerular filtration rate diminished on an average of 11 ml/min while in the other group this function increased on an average of 10 ml/min. Although these changes might be interpreted as explaining the behavior of sodium excretion, statistical analysis of the data nevertheless showed that the variations in glomerular filtration rate were not significant in either group. Furthermore, glomerular filtration rate increased and sodium excretion decreased in three patients of the first group, while glomerular filtration...
Table 1
Mean Arterial Blood Pressure, Renal Hemodynamics, and Renal Resistances in Eleven Patients in Whom Angiotensin Decreased Urinary Excretion of Sodium*

<table>
<thead>
<tr>
<th>Patients</th>
<th>MAP (mm Hg)</th>
<th>GFR (ml/min)</th>
<th>RPF (ml/min)</th>
<th>V (ml/min)</th>
<th>U\text{Na}V (\mu Eq/min)</th>
<th>EF\text{Na} (%)</th>
<th>EF\text{H2O} (%)</th>
<th>RA (dynes • cm⁻² • sec⁻¹)</th>
<th>RV (cm⁻³ • sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.L.</td>
<td>120</td>
<td>140</td>
<td>118</td>
<td>118</td>
<td>249</td>
<td>212</td>
<td>0.37</td>
<td>0.35</td>
<td>44</td>
</tr>
<tr>
<td>R.C.</td>
<td>112</td>
<td>147</td>
<td>144</td>
<td>142</td>
<td>440</td>
<td>278</td>
<td>8.35</td>
<td>1.70</td>
<td>334</td>
</tr>
<tr>
<td>O.C.</td>
<td>91</td>
<td>142</td>
<td>117</td>
<td>124</td>
<td>449</td>
<td>260</td>
<td>9.36</td>
<td>1.23</td>
<td>150</td>
</tr>
<tr>
<td>E.S.</td>
<td>130</td>
<td>160</td>
<td>103</td>
<td>113</td>
<td>480</td>
<td>348</td>
<td>2.84</td>
<td>0.44</td>
<td>74</td>
</tr>
<tr>
<td>E.E.</td>
<td>118</td>
<td>144</td>
<td>93</td>
<td>108</td>
<td>458</td>
<td>375</td>
<td>1.54</td>
<td>0.86</td>
<td>169</td>
</tr>
<tr>
<td>E.H.</td>
<td>130</td>
<td>164</td>
<td>91</td>
<td>48</td>
<td>333</td>
<td>122</td>
<td>4.48</td>
<td>0.67</td>
<td>327</td>
</tr>
<tr>
<td>R.R.</td>
<td>136</td>
<td>152</td>
<td>105</td>
<td>73</td>
<td>382</td>
<td>168</td>
<td>3.36</td>
<td>0.52</td>
<td>124</td>
</tr>
<tr>
<td>G.C.</td>
<td>118</td>
<td>149</td>
<td>95</td>
<td>86</td>
<td>326</td>
<td>137</td>
<td>0.52</td>
<td>0.29</td>
<td>80</td>
</tr>
<tr>
<td>N.C.</td>
<td>141</td>
<td>158</td>
<td>129</td>
<td>117</td>
<td>411</td>
<td>353</td>
<td>1.68</td>
<td>1.82</td>
<td>235</td>
</tr>
<tr>
<td>J.A.</td>
<td>146</td>
<td>202</td>
<td>117</td>
<td>89</td>
<td>320</td>
<td>574</td>
<td>4.39</td>
<td>5.39</td>
<td>277</td>
</tr>
<tr>
<td>Mean</td>
<td>125</td>
<td>157</td>
<td>110</td>
<td>99</td>
<td>396</td>
<td>288</td>
<td>4.56</td>
<td>1.85</td>
<td>224</td>
</tr>
<tr>
<td>Change</td>
<td>+32</td>
<td>-11</td>
<td>-108</td>
<td>-2.71</td>
<td>-75</td>
<td>-0.25</td>
<td>-1.95</td>
<td>+1.3</td>
<td>+0.8</td>
</tr>
</tbody>
</table>

*Each value represents the average of two 30-minute periods.
†C = control; A = angiotensin.
Table 2
Mean Arterial Blood Pressure, Renal Hemodynamics, and Renal Resistances in Sixteen Patients in Whom Angiotensin Increased Excretion of Sodium

<table>
<thead>
<tr>
<th>Patients</th>
<th>MAP (mm Hg)</th>
<th>GFR (ml/min)</th>
<th>RPF (ml/min)</th>
<th>V (ml/min)</th>
<th>U_{NaV} (umEq/min)</th>
<th>EF_{Na} (%)</th>
<th>EF_{H2O} (%)</th>
<th>Renal resistance (dynes \cdot cm^{-5} \cdot sec^{-1} \cdot m^{-3})</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.M.</td>
<td>141</td>
<td>155</td>
<td>119</td>
<td>124</td>
<td>497</td>
<td>415</td>
<td>8.19</td>
<td>7.39</td>
</tr>
<tr>
<td>J.G.</td>
<td>157</td>
<td>177</td>
<td>112</td>
<td>98</td>
<td>415</td>
<td>354</td>
<td>5.45</td>
<td>8.29</td>
</tr>
<tr>
<td>G.G.</td>
<td>145</td>
<td>178</td>
<td>87</td>
<td>109</td>
<td>483</td>
<td>376</td>
<td>3.38</td>
<td>10.90</td>
</tr>
<tr>
<td>E.L.</td>
<td>147</td>
<td>168</td>
<td>52</td>
<td>61</td>
<td>188</td>
<td>145</td>
<td>1.60</td>
<td>3.53</td>
</tr>
<tr>
<td>S.J.</td>
<td>165</td>
<td>207</td>
<td>87</td>
<td>105</td>
<td>261</td>
<td>212</td>
<td>10.33</td>
<td>20.02</td>
</tr>
<tr>
<td>E.G.</td>
<td>162</td>
<td>182</td>
<td>100</td>
<td>132</td>
<td>496</td>
<td>402</td>
<td>2.14</td>
<td>5.94</td>
</tr>
<tr>
<td>R.S.</td>
<td>150</td>
<td>187</td>
<td>76</td>
<td>83</td>
<td>229</td>
<td>179</td>
<td>0.91</td>
<td>6.57</td>
</tr>
<tr>
<td>M.M.</td>
<td>137</td>
<td>170</td>
<td>84</td>
<td>108</td>
<td>271</td>
<td>242</td>
<td>0.93</td>
<td>1.78</td>
</tr>
<tr>
<td>A.C.</td>
<td>164</td>
<td>182</td>
<td>108</td>
<td>103</td>
<td>412</td>
<td>295</td>
<td>15.37</td>
<td>11.21</td>
</tr>
<tr>
<td>L.S.</td>
<td>160</td>
<td>192</td>
<td>80</td>
<td>121</td>
<td>288</td>
<td>346</td>
<td>1.97</td>
<td>15.66</td>
</tr>
<tr>
<td>Y.P.</td>
<td>157</td>
<td>187</td>
<td>106</td>
<td>85</td>
<td>360</td>
<td>204</td>
<td>5.48</td>
<td>11.91</td>
</tr>
<tr>
<td>A.G.</td>
<td>169</td>
<td>200</td>
<td>31</td>
<td>36</td>
<td>152</td>
<td>138</td>
<td>1.23</td>
<td>3.98</td>
</tr>
<tr>
<td>F.T.</td>
<td>140</td>
<td>196</td>
<td>91</td>
<td>90</td>
<td>450</td>
<td>405</td>
<td>5.80</td>
<td>8.13</td>
</tr>
<tr>
<td>R.P.</td>
<td>162</td>
<td>180</td>
<td>173</td>
<td>185</td>
<td>493</td>
<td>471</td>
<td>6.71</td>
<td>17.01</td>
</tr>
<tr>
<td>E.R.</td>
<td>132</td>
<td>168</td>
<td>113</td>
<td>130</td>
<td>310</td>
<td>263</td>
<td>8.18</td>
<td>11.91</td>
</tr>
<tr>
<td>A.M.</td>
<td>110</td>
<td>144</td>
<td>114</td>
<td>124</td>
<td>579</td>
<td>325</td>
<td>0.72</td>
<td>1.04</td>
</tr>
<tr>
<td>Mean</td>
<td>150</td>
<td>180</td>
<td>96</td>
<td>106</td>
<td>368</td>
<td>298</td>
<td>4.90</td>
<td>9.07</td>
</tr>
<tr>
<td>Change</td>
<td>+30</td>
<td>+10</td>
<td>-70</td>
<td>+4.17</td>
<td>+701</td>
<td>+4.78</td>
<td>+3.81</td>
<td>+8.0</td>
</tr>
</tbody>
</table>

*p each value represents the average of two 30-minute periods.
+C = control; A = angiotensin.
Angiotensin produced two different types of response in sodium and water excretion without changing glomerular filtration rate. The upper part represents the changes observed in the 11 patients in whom excretion of sodium and water decreased and the lower part shows the changes in the 16 patients in whom excretion of sodium and water increased.

Another factor that also substantiates the tubular effect of angiotensin is that water excretion and water excretion fraction, which were similar in both groups in the control periods, followed the same pattern as sodium under action of the substance.

When changes in sodium excretion were related to mean arterial blood pressure (fig. 2), it was observed that the decrease in sodium excretion after angiotensin was associated with a mean arterial blood pressure, during the control period, of 136 mm Hg or less in all but two patients (N.C. and J.A.), while the rise in sodium excretion occurred in patients whose control mean arterial blood pressure was more than 136 mm Hg, except in two patients (E.R. and A.M.). These results are in accordance with the findings of Brown and Peart who observed natriuresis under angiotensin in patients with diastolic pressure above 120 mm Hg and antinatriuresis when readings were below this figure.

A direct relation has been shown experimentally between sodium excretion and mean arterial blood pressure when glomerular filtration rate is constant. This may explain the natriuresis observed in the second group when mean arterial blood pressure was raised by angiotensin. However, although the increase in mean arterial blood pressure in the first group was similar, a change in sodium excretion in the opposite direction was observed.

Renal resistances were also studied to find out whether the difference in sodium excretion had any relation to the sensitivity of the intrarenal vessels to the action of angiotensin. The only difference between the groups during the control period was in afferent arteriolar resistance. This observation at first seems to indicate that this discrepancy might be responsible for the results obtained. But this difference between the two groups disappeared under angiotensin. This fact makes it difficult to explain discrepancies in sodium excretion on that basis. No significant differences were found in efferent arteriolar resistances or venular resistances in the two groups.
between the control period and under angiotensin; for this reason, intravascular renal changes apparently had no influence on the two types of response observed.

Our results seem to indicate that increase or decrease in sodium excretion is related to the mean arterial blood pressure before administration of angiotensin but not to the increment in blood pressure produced by the substance.

As in the control period, no differences in glomerular filtration rate between the two groups of patients were found under the action of angiotensin. This function probably remained unchanged in spite of the fact that afferent arteriolar resistance rose markedly inasmuch as both mean arterial blood pressure and efferent arteriolar resistance increased.

Renal plasma flow decreased in both groups which may be explained by the increase in afferent as well as efferent arteriolar resistance.

References

Value of Venous Catheterization: First Efforts of Young Investigators

By the time Joseph Aub studied Physiology in 1911, Cannon had become interested in the effect of epinephrin on the gastrointestinal tract. He invited students of his class to come into the laboratory to try their hands at research if they wanted to... Cannon suggested that Aub and Binger study the influence of smoking on the flow of epinephrin, and the experiment took the form of working with nicotine and cats. A catheter was passed up the femoral vein of the cat until it was opposite the adrenal, then samples of blood were sucked out and tested for the presence of epinephrin, by means of its effect on smooth muscle contraction. In this way it was clearly shown that nicotine stimulated the flow of epinephrin. The first publication of Joseph Aub, with Cannon and Binger, reported this finding in the Journal of Pharmacology and Experimental Therapy (3, 379, 1912).—PAUL ZAMECNIK: Presentation of the Kober Medal for 1966 to Joseph Charles Aub. Trans Ass Amer Physicians 79: 85, 1966.
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Circulation. 1967;35:889-894
doi: 10.1161/01.CIR.35.5.889
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

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