Water and Salt Excretion after Intravenous Salt Load in Hypertensive Subjects


Intravenous salt-loading tests were performed in 20 hypertensive and 31 normotensive subjects. During the following 5 half-hour collection periods both water and salt excretion by the hypertensive subjects was higher than by the normotensive ones. The diuretic response was much more prolonged and more pronounced than the saluretic response and appears to be a primary response to the salt load, characteristic of the hypertensive state. The increased salt excretion is in part to be explained as the consequence of the increased water excretion. At moderate flow rates a salt-retaining mechanism could be demonstrated which is obscured at the higher rates of urinary flow that usually follow the salt load.

An abnormality in the renal excretion of salt in the hypertensive state has been assumed for many years. It has been claimed by some authors that salt retention is a basic physiologic disturbance of the hypertensive state. On the other hand, more recent reports indicate that hypertensive patients in the early stages of their disease and animals with experimental hypertension tend to excrete salt during acute experiments more rapidly than do normal subjects.

Most of these experiments have been carried out under conditions of increased urinary flow after oral or intravenous administration of large amounts of fluid, intravenous administration of hypertonic salt solutions, or osmotic diuresis caused by mannitol given intravenously. Since the rate of urinary flow may influence the rate of excretion of solutes, it appeared to us that the excretion of salt in the hypertensive as compared with the normal state could be evaluated only in terms of the simultaneous excretion of water.

In the following study the differences in the excretion of both water and salt after an intravenous load of hypertonic saline between normal subjects and patients with hypertension are analyzed.

Material and Methods

The subjects were 20 hypertensive patients in the early stages of their disease and without complications, as judged from their histories and physical status. The control group comprised 31 patients without hypertension, cardiovascular, renal, or hepatic disease. The subjects in both groups had normal urinary findings, normal urinary concentrating power, and creatinine clearances within the normal range. The subjects in both groups were not restricted in their intake of salt during the days preceding the tests.

Salt-loading tests were performed in the morning after a very light breakfast. After urine collection for 30 minutes through an indwelling catheter, 5 Gm. of sodium chloride per square meter of body surface were given intravenously as a 5 per cent solution over a period of 30 minutes. The urine was collected during this period and for 5 more consecutive periods of 30 minutes each. The patients were allowed to drink up to 200 ml. of water if they desired. Blood and urine samples were obtained before the intravenous salt solution was given, and at the end of the last collection period, for the determination of sodium chloride and creatinine. The urinary volume and the excretion of sodium and chloride during the 5 periods following the end of the intravenous infusion were compared in the 2 groups.

Results

The urinary flow was significantly higher in the hypertensive group than in the normal during each 30-minute collection period after
administration of hypertonic saline. The excretion of sodium and chloride was also higher in the hypertensive group than in the normal subjects. However, this difference was less pronounced than the difference in water excretion, and was significant only during the first 2 collection periods after infusion (table 1).

In order to find out if the excretion of salt is related to the rate of urinary flow in the same way in both groups of subjects, the excretion of sodium and of chloride was plotted against the corresponding urinary flow. Separate analyses were made for the hypertensive and the normotensive subjects. Only the 2 periods immediately following the end of the sodium chloride infusion were chosen because the effect of secondary compensatory mechanisms might subsequently obscure the relationships (figs. 1 and 2).

For the plotting a method was chosen that is based on the work of Dole:21 if logarithm of the relative clearance of any substance

\[ \log \frac{\text{clearance x}}{\text{clearance inulin}} \]

reciprocal rate of urinary flow \((1/v)\), an approximately straight or slightly curved line results, the slope of which is a measure of its tubular reabsorption.

When our data were plotted in this manner, a definite positive relationship became evident between the urinary flow and the clearance of sodium and chloride in both

### Table 1.—Urinary Responses after Intravenous Sodium Chloride Load

<table>
<thead>
<tr>
<th>Urinary volume (ml./min./M.² body surface area)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>Mean</td>
<td>0.76</td>
<td>0.86</td>
<td>0.91</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>0.29</td>
<td>0.33</td>
<td>0.39</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>31</td>
<td>31</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Hypertensive subjects</td>
<td>Mean</td>
<td>1.72</td>
<td>1.75</td>
<td>1.67</td>
<td>1.51</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>1.26</td>
<td>1.27</td>
<td>0.92</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

| Sodium excretion (mEq./min./M.² body surface area) | Mean | 0.186 | 0.209 | 0.219 | 0.220 | 0.211 |
|--------------------------------------------------|--------|--------|--------|--------|--------|
| Normal subjects | S.D. | 0.092 | 0.073 | 0.097 | 0.084 | 0.087 |
| | n | 31 | 31 | 30 | 30 | 25 |
| Hypertensive subjects | Mean | 0.302 | 0.286 | 0.286 | 0.242 | 0.240 |
| | S.D. | 0.228 | 0.198 | 0.151 | 0.128 | 0.135 |
| | n | 20 | 20 | 20 | 20 | 17 |
| p | <0.02 | 0.05 | <0.05 | 1.31 | 0.85 |

| Chloride excretion (mEq./min./M.² body surface area) | Mean | 0.187 | 0.204 | 0.213 | 0.189 | 0.201 |
|---------------------------------------------------|--------|--------|--------|--------|--------|
| Normal subjects | S.D. | 0.084 | 0.071 | 0.074 | 0.084 | 0.082 |
| | n | 31 | 31 | 30 | 30 | 25 |
| Hypertensive subjects | Mean | 0.285 | 0.270 | 0.260 | 0.223 | 0.223 |
| | S.D. | 0.183 | 0.160 | 0.122 | 0.110 | 0.120 |
| | n | 20 | 20 | 20 | 20 | 17 |
| p | <0.02 | 0.05 | <0.4 | <0.1 | <0.5 |

*The absolute clearances of sodium and chloride were plotted instead of their relative clearance because inulin clearances were not performed. However, since in most instances creatinine clearances were calculated and found to be unchanged during the first 2 periods after infusion as compared with a control period before infusion, and since the serum concentrations of sodium and chloride were found essentially unchanged throughout the experiment, it can be assumed that the substitution of absolute clearance figures for relative clearances did not entail a significant or systematic error.
our data, on the assumption that the curves may be represented with reasonable accuracy by straight lines, and the differences in the slopes of the regression lines for the hypertensive and the normotensive subjects were found to be statistically significant: $t_{Na} = 4.0$; $t_{Cl} = 4.85$.

Furthermore, the curves, when superimposed, crossed each other at points corresponding to flow rates of about $2$ ml. per minute ($1/v = 0.5$). At higher rates of flow the

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**Fig. 1** Top. Clearance of sodium ($C_{Na}$) in ml./min./M.$^2$ (ordinate) as function of flow in ml./min./M.$^2$ (abscissa).

**Fig. 2** Bottom. Clearance of chloride ($C_{Cl}$) in ml./min./M.$^2$ (ordinate) as function of flow in ml./min./M.$^2$ (abscissa).

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rours (figs. 1 and 2). High urinary flow rates were associated with high excretion of sodium and chloride; with decreasing urinary flow the amounts of sodium and of chloride stealing tubular reabsorption and appearing in the urine became progressively smaller. The plots for the normotensive and hypertensive subjects showed marked differences in various aspects, as seen from the curves. The dotted (by inspection) through the plotted points. Regression lines were calculated from
sodium and chloride clearances in the hypertensive subjects were higher than in the normotensive ones; at medium and low flow rates the hypertensive subjects excreted less salt than did the normotensive subjects.

DISCUSSION

The data presented show that hypertensive subjects react to intravenous administration of hypertonic salt solution with a greater output of water, as well as of salt, than do normal subjects. In similar experiments other workers also found increases both in water and in salt excretion by hypertensive subjects. However, the possible relationship between the increased diuresis and saluresis has not been clearly formulated.5, 7, 8, 15 Most workers seem to assume that the increased rejection of salt by the renal tubules is the cause of the increased rejection of water. This assumption does not seem to be valid, however, for those experiments in which higher flow rates were obtained in hypertensive than in normotensive subjects by the administration of isotonic or solute-free fluids.3, 9, 10 The increased diuretic response in these experiments cannot possibly be the result of increased solute excretion, but must be regarded as a primary reaction of the hypertensive subjects to the experimental procedure.

On the other hand, the increased excretion of salt in all the reported experiments can be explained, at least in part, as the consequence of the high rates of urinary flow. The existence of such a relationship between urinary flow and salt excretion is apparent from the figures correlating the data of our experiments. A similar interpretation has been given by various workers to the increased sodium and chloride excretion observed during osmotic and water diuresis in man and in animals.16–19 Moreover, a positive correlation between urinary flow and solute excretion has also been found for substances which were present only in small amounts in the glomerular filtrate, and which therefore could not in themselves constitute a solute load causing osmotic diuresis.20 It has been suggested that the increased diuresis sweeps salt out of the proximal tubule faster than the distal tubule can handle it.22 It seems reasonable therefore to assume that the renal response of hypertensive subjects to the various experimental stimuli is primarily one of increased urinary output, and that the increase in salt excretion is, at least in part, the consequence of the increased rate of urinary flow. Moreover, it is possible that the more rapid excretion of salt is an additional, separate expression of the same regulatory mechanism that causes the increased diuretic response in hypertensive subjects. The basic physiologic mechanism causing increased diuresis and—directly or indirectly—increased saluresis may be a reaction to the overexpansion of the extracellular fluid space. This mechanism, then, appears to be brought into action more readily in the hypertensive than in the normotensive state.

In contrast to the increased salt excretion under conditions causing high rates of urinary flow, our figures show that at moderate or low flow rates—below 2 ml. per minute—the hypertensive subjects excreted less salt than did the normotensive subjects at the same rates of flow. This phenomenon indicates a more complete tubular reabsorption of salt in the hypertensive subjects and may be a manifestation of the postulated salt retaining mechanism in the hypertensive state. As can be seen from our data, this mechanism is apparent only at low or moderate flow rates; under experimental conditions leading to high rates of urinary flow, it is abolished or obscured by the increased saluresis accompanying the increased diuresis.

A comprehensive description of the behavior of hypertensive subjects, as compared with normotensive ones, would therefore have to include their increased diuretic and saluretic response to salt and fluid loads, as well as a relative salt retention. The increased diuresis appears to be a more constant and a more pronounced feature than the increased salt excretion. The relative salt retention becomes manifest only at urinary flow rates up to about 2 ml. per minute and becomes
obscured under conditions causing higher rates of urinary flow.

Summary

In acute salt-loading experiments, hypertensive subjects excreted both water and salt at significantly higher rates than normal subjects. The difference in the diuretic response was greater and more pronounced than the difference in the saluretic response.

This increased salt excretion by hypertensive subjects may be explained in part as the consequence of the increased rate of water excretion, and in part as the direct effect of a regulatory mechanism, which causes both diuresis and saluresis and which is more active in the hypertensive state.

Although the hypertensive subjects as a group excreted salt more rapidly than did the normotensive ones, at lower rates of urinary flow, up to about 2 ml per minute, the salt excretion by the hypertensive subjects was less than by the normotensive ones. This observation is interpreted as the manifestation of a "salt-retaining mechanism" in the hypertensive state, which becomes obscured under conditions causing increased diuresis.

Acknowledgment

The valuable technical assistance of Mrs. L. Ullmann is gratefully acknowledged.

Summary in Interlingua

In experimentos a cargation acute con sal, subjectos hypertensive excerneva aqua e sal con significativemente plus alte intensitates que subjectos normal. Le differentia inter le responsas diuretic esseva plus grande e plus pronunciata que le differentia inter le responsas saluretic.

Le augmentate excretion de sal in subjectos hypertensive pote esser explicate in parte como le consequentia del intensificate excretion de aqua e in parte como le effecto directe de un mechanismo regulatori que initia le diuresis e le saluresis e que es plus active in le stato de hypertension.

Ben que le subjectos hypertensive, considerate como un gruppo, excerneva sal plus rapidemente que le subjectos normotensive, in caso de plus lente fluxos de urina, i.e. usque a un volumine de circa 2 ml per minuta, le excretion de sal per le subjectos hypertensive eseva inferior a illo de subjectos normotensive. Iste observation es interpretate como le manifestation de un "mechanismo de retention de sal" in le stato de hypertension. Iste manifestation es obscuret sub conditiones que causa un augmento del diuresese.

References

11. FRIEDMAN, S. M., HINKE, J. A. M., AND


The author reviews the evidence for the complementary roles of thrombogenic and mechanical factors in atherosclerosis. The mechanical hypothesis is that impairment of the elasticity or flexibility of an artery must lead to the structural disorganization that is seen in atherosclerosis. Atheroma results from the tearing and destruction of tissues resulting from the thickening and loss of elasticity of the intima. Arterial narrowing results from mural thrombosis formation followed by endothelial proliferation and incorporation in the wall becoming a fibrous thickening of the intima. One result is a loss of elasticity and flexibility and, in the case of large areas, dilatation of the vessel. Intimal hemorrhage, frequently found when carefully sought, provides support for the mechanical hypothesis, since it indicates that the forces disrupting the intima are active in living tissues. Many of the fatty changes of atherosclerosis according to this hypothesis are the products of hemmorhages or thrombi. But intimal damage also results in reduced tissue pressure at the points of loosening with resultant drawing of lipid-rich body fluids into these spaces. The genesis of atherosclerosis is thus traced from initial damage to the vessel wall, thrombosis, intimal thickening, and further vascular disruption. The dangers of atherosclerosis result from loss of control of the factors in blood or tissue that regulate thrombosis.

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