Studies on the Mechanism of the Abnormal Sodium Excretion in Arterial Hypertension

By Irwin B. Hansen, M.D., Edmond Ricanati, M.D., and Nathan Polasky, M.D.

It has been demonstrated that patients with essential hypertension excrete an intravenous sodium load more rapidly than do individuals with normal blood pressure. The data suggest that this abnormality results from the elevated blood pressure. Among the several explanations that have been offered for this excretory alteration are unspecified extrarenal factors and such intrarenal disturbances as reduction in renal blood flow with elevated filtration fraction, increased renal intravascular pressure, and altered tubular function.

While the available evidence would strongly focus on a renal mechanism, none of the previously suggested possibilities has received experimental confirmation. To obtain a better understanding of the nature of the sodium excretion pattern in hypertension, studies relating sodium and water excretion, glomerular filtration rate (GFR), renal plasma flow (RPF), and tubular excretory capacity for sodium para-aminohippurate (TmPAH) have been performed in subjects with normal blood pressure and with labile and essential hypertension. In addition, consideration has been given to the temporal relationship between the observed elevation of blood pressure and the appearance of renal functional abnormalities.

Materials and Methods

The studies were performed on individuals with labile and essential hypertension and healthy subjects with normal blood pressure. Urinalysis, phenolsulphonphthalein excretion, urea clearance, and intravenous pyelography were normal in all the hypertensive patients. There was no evidence of abnormal adrenal function or cardiac decompensation associated with the high blood pressure. The degree of retinopathy was grade II or less. Except when the effect of a low sodium intake was being studied, all subjects received a regular hospital diet which contained 7 to 9 Gm. of salt per day. Although the addition of extra salt was permitted for palatability, the amounts consumed by the hypertensive and control groups were comparable. None of the patients with elevated blood pressures was receiving antihypertensive drug therapy.

All procedures were carried out at approximately the same time in the morning with the subjects in the supine position. Urine specimens were collected through multiholed soft rubber urethral catheters with air washouts. Blood samples were drawn from arm veins without stasis. The samples were heparinized and kept on ice until the plasma could be separated for analysis. Urines and plasma were analyzed as soon as possible after collection. If for any reason there was a delay, the specimens were frozen.

Intravenous Salt-Loading Studies

Water and food were withheld from the preceding midnight until the completion of the study. At the beginning of the procedure a 60-minute urine sample was collected. Then the patient received an intravenous infusion of 100 ml. of 5 per cent sodium chloride per M.² of body surface area over a 25-minute period. Urine specimens were obtained at 30 and 60 minutes after the start of the infusion. Blood samples were drawn during the control period and at the midpoint of all subsequent urine collections.

Hydration Studies

Food and fluids were withheld from midnight preceding the study. In the morning the patients received 1,000 ml. of water orally over a 15-minute period. This positive balance of a liter was maintained throughout the procedure by replacing urinary losses with water by mouth. When urine

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flow had reached maximum levels, three 10-minute specimens were collected. A blood sample was obtained after the final urine collection.

The patients then received aqueous vasopressin (Pitressin)* (0.3 mU./Kg.) intravenously. The degree and duration of antidiuresis were noted by the collection of appropriately spaced urine samples. A blood sample was obtained before the administration of vasopressin, at the time of minimum urine flow and again at the time of final peak diuresis.

**Dehydration Studies**

Except for a dry supper consisting of hamburger, toast, jam and a cookie, the subjects received nothing by mouth for approximately 20 hours prior to the study. At the start of the procedure an intravenous infusion of 200 mU. per hour of aqueous vasopressin in isotonic saline was begun and delivered at a constant rate of 0.38 ml. per minute for the remainder of the study. Urine specimens were then obtained at 30-minute intervals for two hours and at the end of the third hour. They were collected directly into graduates and terminated with air washouts. Blood samples were drawn at the midpoints of the urine periods.

Similar studies were repeated after the patients had been on a 200-mg. sodium diet for 4 to 6 days.

**Measurement of GFR, RPF, and TmPAH**

No special dietary restrictions were imposed. On the morning of the study breakfast was withheld and the patients received a glass of water by mouth, followed by half a glass every half hour for the remainder of the procedure to assure adequate hydration. After a control venous blood and urine sample had been obtained, an intravenous priming dose of inulin (50 mg./Kg.) and para-aminohippurate (PAH) (8 mg./Kg.) was administered. A sustaining infusion of these same substances followed at rates calculated to equal their renal clearance. A period of 40 minutes was allowed for equilibration. Three urine specimens with appropriate blood samples were then collected and used for the measurement of filtration rate and renal plasma flow.

TmPAH was determined by the administration of an additional priming dose of PAH (160 mg./Kg.) to raise the plasma level above that required for tubular saturation. This concentration was maintained by a sustaining infusion of PAH. After 40 minutes for equilibration, three urine and blood samples were collected.

Serum and urine sodium and potassium were determined with an internal-standard flame photometer. Creatinine was measured by the method of Folin and Wu10 as modified by Phillips.11 To assure complete recovery of creatinine, proteins were precipitated at pH 2 by the procedure described by Owen et al.12 Inulin was determined by the Rolf, Surtshin, and White13 modification of the method of Alving, Rubin, and Miller14 and para-aminohippurate by that of Smith et al.15

**Results**

**Intravenous Salt-Loading Studies**

Figure 1 shows the effect of an intravenous load of 5 per cent saline on sodium excretion in subjects with normal blood pressure and with labile and essential hypertension. The per cent infused sodium excreted during the first hour after the start of the infusion was directly related to the height of the blood pressure, being 2.2 per cent for the control group as contrasted to 7.4 per cent (p > .1) for the labile and 13.3 per cent (p < .01) for the essential hypertensive groups.

**Hydration Studies**

The effects of hydration were studied in these same individuals on a separate occasion during a maintained positive water balance of one liter (table 1). Urinary sodium concentration and excretion were increased in all hypertensive subjects, paralleling the elevation in blood pressure. The same pattern was noted for urine osmolality and could be explained by the changes in the sodium fraction.

Urine flow, creatinine clearance, free water clearance, potassium, and urea excretion were not significantly different in the three groups.

The response to exogenous aqueous vasopressin was also measured in these subjects (table 2). At the height of the water diuresis 0.3 mU. per Kg. vasopressin was administered intravenously, and the degree and duration of antidiuresis were observed. Urine flows prior to hormone administration did not vary significantly between the subjects with normal and elevated blood pressures. Following the administration of vasopressin, the rate of flow decreased 90.9 per cent in the control group but only 81 per cent in the essential hypertensive group (p < .01). This diminished antidiuretic response was associated

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*Lot no. 184 Parke Davis and Co. was used in all studies in which the effects of vasopressin were tested.
### Table 1

<table>
<thead>
<tr>
<th></th>
<th>No. of subjects</th>
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<th>Labile hypertension Range</th>
<th>Essential hypertension Range</th>
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The effect of prolonged fluid restriction on the solute and water excretion of subjects with normal blood pressure and with labile and essential hypertension was similar for the three groups. Dehydration Studies

The effect of an increase in osmolal clearance of from 1.94 to 3.95 ml per min. Despite a 50 per cent increase in solute output, the decrease in urine flow was not significant in normal subjects. Furthermore, at comparable levels of solute output, the decrease in urine flow was less in patients 13 and 15 with essential hypertension than in OR and RS with labile hypertension.

The figures in parentheses indicate the number of individuals studied. The vertical lines drawn through the bars represent the range of values for each group.

![Figure 1](image-url)
Table 2

Response to Vasopressin

<table>
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<th>Patient</th>
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<th>Mean BP* mm. Hg</th>
<th>Maximum diuresis Urine flow ml/min./1.73m.²</th>
<th>Osmolar clearance UV/P ml/min./1.73m.²</th>
<th>Maximum Antidiuresis Urine flow ml/min./1.73m.²</th>
<th>Percent fall</th>
<th>Time min.</th>
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</table>

*Mean blood pressure = systolic blood pressure + diastolic blood pressure

represent the average of five urine collection periods. This manipulation was thought justified since all studies were performed under comparable conditions and the individual values did not differ appreciably.

The patients with labile hypertension showed a lower urine osmolality, 818 mOsm. per Kg. (p < .05), than the control group, 884 mOsm. per Kg. This dilution was accompanied by a slight but insignificant decrease in potassium concentration. No change in urine flow and sodium, potassium, and urea excretion was noted. In the group with essential hypertension urine osmolality was further decreased, 753 mOsm. per Kg. (p < .01), indicating a more marked impairment in urinary concentrating ability. This change was reflected in a higher urine flow, 1.03 ml. per minute, as compared with 0.62 ml. per minute for the normotensive subjects. The urinary concentrations of potassium and urea were diminished, but not that of sodium. Sodium excretion was 63 per cent higher than for the controls, while no significant differences were noted for potassium and urea. Osmolal excretion was also increased for the hypertensive group as a whole.

Mean endogenous creatinine clearances were comparable in all three groups.

To determine whether the impairment of urinary concentrating ability associated with hypertension could result from diminished proximal tubular reabsorption of sodium and a resulting osmotic diuresis, similar measurements were made during the administration of a 200-mg. sodium diet. The data for 6 hypertensive and 4 control subjects are presented in table 4. Following salt restriction, the mean urinary solute concentration fell 10 per cent in the normals and 7 per cent in the group with hypertension. This pattern was observed in all subjects except one of.
the hypertensives (M. McC.). Urine flow and sodium excretion, though higher in the subjects with hypertension while on a regular diet, fell proportionately in both groups when sodium intake was restricted. Urine urea concentration increased and excretion fell. The diminished excretion was correlated with the decrease in urine osmolality.

**Measurement of GFR, RPF, and TmPAH**

Whenever possible, glomerular filtration rate, renal plasma flow, and TmPAH were determined on the same subjects used for the hydration studies (fig. 2). TmPAH and GFR remained within the normal range irrespective of the blood pressure levels. Filtration fraction (FF) increased with the blood pressure as a result of the depression of RPF.

![Figure 2](http://circ.ahajournals.org/)

**Table 3**

<table>
<thead>
<tr>
<th>Response to Dehydration</th>
<th>Normal</th>
<th>Labile Hypertension</th>
<th>Essential Hypertension</th>
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<td>140-220</td>
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<tr>
<td>Mean diastolic pressure</td>
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<tr>
<td>Mean age</td>
<td>60</td>
<td>60</td>
<td>60</td>
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<tr>
<td>Mean GFR (ml/min/1.73 M²)</td>
<td>110.7</td>
<td>102.1</td>
<td>90.1</td>
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<tr>
<td>Mean RPF (ml/min/1.73 M²)</td>
<td>157.28</td>
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<td>Mean TmPAH (mg/min/73 M²)</td>
<td>1.6</td>
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</table>

![Figure 2](http://circ.ahajournals.org/)

**Relationship of Blood Pressure to TmPAH, GFR, RPF and FF.**

Mean blood pressure =

$$\text{systolic blood pressure} + \text{diastolic blood pressure}$$

The vertical lines drawn through the bars represent the range of values for each group.
# Table 4

**Effect of Low Sodium Diet on Response to Dehydration**

<table>
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<tr>
<th>Patient</th>
<th>Age</th>
<th>Sodium intake gm/day</th>
<th>Creatinine clearance ml/min/1.73m²</th>
<th>Urine flow ml/min/1.73m²</th>
<th>Sodium U, μeq/min/1.73m²</th>
<th>Potassium UV μeq/min/1.73m²</th>
<th>Osmolality U mOsm/Kg.</th>
<th>UV μOsm/min/1.73m²</th>
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<th>Urea μM/min/1.73m²</th>
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ABNORMAL SODIUM EXCRETION IN HYPERTENSION

Discussion

The results of these studies indicate that individuals with arterial hypertension but without overt clinical evidence of impaired renal function have abnormalities of both sodium excretion and urinary concentrating and diluting ability.

Among the possible explanations for these excretory changes is a solute diuresis due to the high salt output. It has recently been demonstrated\textsuperscript{16-19} that the regulation of urinary solute concentration is dependent upon a countercurrent mechanism in which sodium without water is transported from the tubular lumen to interstitium along the ascending limb of the loop of Henle. In the presence of antidiuretic hormone, water moves passively from the collecting duct into the hypertonic interstitial fluid, resulting in the formation of a concentrated urine. Without vasopressin the tubular fluid remains dilute and a urine of low osmolality is excreted. A greater solute load reaching the collecting duct under conditions of water deprivation would reduce the per cent of water diffusing into the medullary interstitium and limit concentrating ability. During hydration, on the other hand, an additional volume of proximal tubular fluid reaching the distal nephron would increase urinary sodium concentration and excretion. The abnormal excretory pattern observed in the hypertensive patient could, therefore, be attributed to the delivery of an increased volume of isosmotic fluid from the proximal to the distal segment. The supplementary fluid load would logically result from diminished proximal tubular sodium reabsorption since there is no significant difference in glomerular function between the subjects with normal and elevated blood pressures.

There are several observations, however, that do not support this interpretation. Under conditions of hydration, despite increased solute excretion the hypertensive subjects had urine flows and free water clearances within the normal range. This is in contrast to the direct relationship between solute and water excretion noted in hydrated normal subjects by Kleeman et al.,\textsuperscript{20} which they attributed to the movement of supplementary isosmotic fluid from the proximal to the distal tubule.

Additional evidence against a defect in the proximal part of the nephron is the similar response of hypertensive and normotensive subjects to a 200-mg. sodium diet under conditions of dehydration. If the inability of the hypertensive patient to concentrate urine normally resulted from excessive delivery of proximal tubular fluid to the distal nephron, then improvement should be noted when sodium excretion is decreased. Such a change did not occur. Rather, if anything, a slight fall in urine osmolality occurred in the control group and in 5 of the 6 patients with high blood pressure. This decrease probably reflects the diminished urea excretion associated with the special diet and the slight fall in filtration rate. It is unlikely that the diminished filtered load of sodium and its enhanced reabsorption by the proximal tubule resulting from the low salt intake failed to provide sufficient amounts of this ion for normal operation of the countercurrent system. This conclusion is supported by the observations of others\textsuperscript{21, 22} in which comparable diets, reductions in filtration rate of 10 to 30 per cent, and even lower rates of sodium excretion were associated with normal or increased concentrating ability.

The response to antidiuretic hormone following a water load also fails to support the proposed concept of altered proximal tubular function. If this mechanism applied, then an inverse relationship should be observed between osmolar clearance and the per cent fall in urine flow following vasopressin. Despite a significant increase in solute excretion in the labile hypertensive group, the antidiuretic response was normal. Furthermore, at comparable levels of solute clearance, there was a lesser decrease in urine flow in the patients with essential hypertension than in those with labile blood pressure.

Further indication that there is no significant deterioration of proximal tubular func-
tion is the normal TmPAH (fig. 2). Caution must be exercised, however, in extrapolating from one transport system to another. While the normal TmPAH would support the concept of a functional disturbance in the distal part of the nephron, there is no conclusive evidence that the transcellular movements of sodium and PAH are related. It has been noted, for example, by Berliner et al. that in man mercurial diuretics depress both TmPAH and sodium reabsorption. This combined effect has not, however, been observed in the dog.

A second possibility that could explain the hypertensive pattern of sodium and water excretion is an impairment of sodium transport from the ascending limb of Henle's loop to the medullary interstitium. This would reduce urinary osmolality in the dehydrated state by limiting the passive diffusion of water out of the collecting duct. It would also lead to the increased urinary sodium concentration and excretion observed under conditions of water loading. This concept cannot be excluded by our data. Opposed to it, however, is the capacity of the hypertensive subjects to generate a normal quantity of free water. Also, there would be implied the unlikely situation of a selective lesion of the ascending limb of Henle's loop that would progressively worsen as the arterial pressure rose and improve as the blood pressure was reduced by antihypertensive agents.

Another mechanism that can satisfactorily explain the observed excretory abnormalities is an acceleration of renal medullary blood flow resulting from the hypertension. The vasa recta play a significant role in the regulation of urinary solute concentration. Through their hairpin configuration they act as a countercurrent exchanger. The osmolality of the medullary fluid is, therefore, related to the blood flow through these vessels.

It has been shown by Selkurt that the dog kidney responds to an elevation in perfusion pressure by an increased excretion of sodium and water. More recently, Thurau and his colleagues measured the effect of increasing the perfusion pressure on the medullary and cortical blood flow through the dog kidney. As the pressure was raised, the medullary circulation acted as a pressure-dependent system while that of the cortex remained relatively constant, exhibiting autoregulation. Urine flow increased concurrently with the rising perfusion pressure. This pressure diuresis was believed to result from the augmented blood flow through the vasa recta, which by removing solute from the medulla impaired the efficiency of the countercurrent system. Since only about 1 per cent of the renal blood flow normally perfuses the medulla, a 100 per cent increase in the medullary component would only increase total flow by 1 to 2 per cent. This would not be detected by clearance measurements and yet could significantly influence the urine concentrating mechanism.

It appears reasonable to visualize an analogous situation for the kidneys of the hypertensive patient. The high arterial pressure would result in an increased medullary blood flow. Solute concentration in the adjacent interstitial tissue would be reduced and concentrating ability impaired. In addition, the glomerular filtration rate of the nephrons supplied by this circulation would be increased. This would lead to a greater filtered load of sodium and an accelerated urine flow through the loop of Henle, which would result in the abnormally high sodium excretion associated with hypertension as well as the elevated sodium concentration observed during hydration. Total filtration rate of the kidney would not be raised significantly because of the relatively small fraction of the renal blood flow perfusing the juxtamedullary glomeruli.

In support of this concept is the observation that the disturbance of sodium and water excretion occurs in the absence of any overt evidence of renal disease when other measures of kidney function are intact. There is, furthermore, a direct relationship between the degree of abnormality of sodium and water excretion and the height of the blood pres-
ABNORMAL SODIUM EXCRETION IN HYPERTENSION

875

sure. The hypertensive pattern of sodium excretion is not peculiar to essential hypertension but is also associated with the elevated blood pressure in Cushing’s syndrome and pheochromocytoma. In addition, the abnormal natriuresis appears after the development of hypertension and is improved when the arterial pressure is reduced. The beneficial effect of lowering the blood pressure is not related to any specific agent or type of hypertension since it has been noted following various antihypertensive agents and in a patient with Cushing’s syndrome whose blood pressure fell significantly after adrenalectomy.

Additional corroboration is provided by the studies of Abbrecht and Malvin in which during osmotic diuresis in the dog high flow rates of fluid through the loop of Henle prevent the establishment of a normal counter-current gradient and result in an elevated urine sodium concentration and excretion. Also of relevance are the observations of Nickel et al. that a 25 to 50 mm. Hg increase in systolic pressure produced by the infusion of ephedrine and norepinephrine in normal human subjects was associated with an increase in sodium output when filtration rate and renal blood flow remained essentially unchanged. More recently, it has been reported that an augmented natriuresis occurs in normotensive subjects whose blood pressures have been elevated with metaraminol.

Summary

Individuals with uncomplicated essential hypertension exhibit an abnormally high excretion of sodium and an associated impairment of urinary diluting and concentrating ability. Various possibilities have been considered to explain these related excretory changes including a solute diuresis resulting from diminished proximal tubular reabsorption of sodium, a reduction in sodium reabsorption from the ascending limb of the loop of Henle, and an increase in medullary blood flow. Evidence has been presented that does not support a defect in the sodium transport mechanism. On the other hand, the observed excretory abnormalities, when considered in terms of the reported pressure-dependent nature of the medullary circulation, could result from an increase in blood flow through the vasa recta secondary to the arterial hypertension.

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References


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