The Influence of Hypertonic Saline Infusions Upon the Fractional Reabsorption of Urate and Other Ions in Normal and Hypertensive Man

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SUMMARY

Renal hemodynamics and the excretion rates of six ions were studied in a group of 24 normotensive and hypertensive subjects during expansion of extracellular fluid volume (ECF) with intravenous infusions of hypertonic saline. In response to the 2.5% saline infusions arterial blood pressure did not change from control values, but glomerular filtration rate increased, and renal vascular resistance decreased.

Accompanying these hemodynamic alterations the urinary excretion rates of sodium, calcium, magnesium, potassium, chloride, and urate increased significantly. Net fractional reabsorption of the six ions fell significantly below control values. The induced changes in net Ca, Mg, K, Cl, and urate reabsorption in all the subjects were directly and significantly related to the simultaneous depression of Na reabsorption.

The data indicate that increased excretion and net tubular rejection of urate accompany depression of tubular sodium reabsorption during hypertonic saline infusions in normal and hypertensive man. The nonspecificity of depressed fractional ion reabsorption during the infusions is compatible with the hypothesis that physical forces which alter fluid uptake by peritubular capillaries determine to a significant extent the natriuretic response of the human nephron to hypertonic saline infusions. Alternatively, if a natriuretic hormone elicited by ECF volume expansion in man accounts for the depressed fractional Na reabsorption, the data imply that directly or indirectly this substance inhibits net fractional reabsorption of a variety of other ions.

Additional Indexing Words:
Renal hemodynamics Natriuresis Urinary excretion of electrolytes

A NUMBER of investigations have indicated that during the expansion of extracellular fluid (ECF) volume induced by intravenous infusions (saline, albumin, dextran, or dilute dextrose) a depression of fractional sodium reabsorption by the renal tubules occurs which cannot be explained solely by changes of glomerular filtration rate or of aldosterone activity. Although depressed net sodium transport during ECF volume expansion has been localized by clearance and micropuncture studies predominantly to proximal tubules, nevertheless, significant similar changes have been localized to more distal portions of the nephrons in animals and in hypertensive patients. The relevance of this renal response to ECF volume expansion to the pathogenesis of edema has been suggested by the finding that...
a normal fall in proximal sodium transport did not occur during saline infusions in animals with partial thoracic caval ligation, an experimental procedure which induces the formation of edema and ascites.

The present studies were undertaken to clarify further the responses of the human nephron to acute expansion of extracellular fluid volume. Studies of osmotic diuretics in man and the dog have suggested a link between the tubular reabsorption of sodium, calcium, and magnesium; reports of hyperuricemia after salt restriction or diuretic administration in man have raised the possibility of a similar association between sodium and urate reabsorption. Because the simultaneous excretion patterns of multiple ions have not been previously examined during saline loading in man, the urinary excretion rates of sodium, potassium, calcium, magnesium, chloride, and urate were measured in response to infusion of 2.5% saline.

The protocol was designed to compare the excretion pattern of each ion to that of sodium. To insure high rates of sodium excretion, hypertonic rather than isotonic saline infusions were administered, and hypertensive subjects were included in the study group because hypertensives frequently exhibit an exaggerated natriuresis in response to infusions which expand ECF volume. The data demonstrate nonspecific loss of many ions during hypertonic saline loading and indicate a relationship between net fractional reabsorption rates of sodium and urate during the infusions.

**Methods**

Twenty-four renal clearance studies were performed in nine normotensive subjects and 15 hypertensive patients. Seven of the normotensives were normal volunteers and two were patients with scleroderma without urinary findings suggestive of renal disease. Thirteen of the hypertensives had essential hypertension and two suffered from hypertension secondary to chronic inactive pyelonephritis. All of the normotensive subjects and 12 of the hypertensives consumed a normal sodium diet; three hypertensives voluntarily restricted their salt intake. None of the patients received any medications other than occasional bedside sedation with barbiturates. None had papilledema, congestive heart failure, or a blood urea nitrogen level above 26 mg%.

All experiments were performed at the same early morning hour with the subjects fasting and resting quietly in bed. Water diuresis was introduced by oral administration of 750 ml of water during the hour prior to the infusion and was maintained by intravenous administrations of a 5% dextrose solution (D/W) at a rate of 9 ml/min, held constant by a motor-driven pump. Urine collections were made and discarded until a steady state of urine flow was achieved. Three or four 10-minute clearance periods were then obtained. Subsequently, an infusion of 2.5% saline was substituted for 5% D/W at a rate of 15 ml/min; clearance periods were then obtained every 15 to 20 minutes for the next 2 to 3 hours.

Venous blood samples were collected at the midpoint of each period through an indwelling needle. Urine was collected continuously via an indwelling sterile catheter except in three normotensive young male subjects for whom spontaneous voiding presented no significant difficulty. Blood pressure was measured from the arm during the clearance periods with a standard cuff mercury sphygmomanometer. No subject developed pulmonary congestion during the infusions, and in none was a significant increase in cardiac rate observed.

The rates of glomerular filtration (GFR) and of effective renal plasma flow (ERPF) were determined from the clearance of inulin (IN) and of para-aminohippuric acid (PAH) by technics previously described. Urate was measured by the method of Praetorius. Sodium and potassium concentrations in plasma and urine were determined with an Instrumentation Laboratories flame photometer. The concentrations of calcium and magnesium in urine and in trichloracetic acid plasma filtrates were measured with a Perkin-Elmer atomic absorption spectrophotometer after addition of lanthanum chloride. Chloride concentrations were measured by potentiometric titration with a Cotlove chloridometer. Urine and plasma total solute concentrations were measured with an Advanced Instruments osmometer.

**Calculations**

Mean arterial blood pressure was calculated as the average of systolic and diastolic pressures in mm Hg. Effective renal blood flow (ERBF) was calculated as the clearance of PAH divided by 1-Hct. Renal vascular resistance in dynes sec cm⁻⁵ was calculated from the formula:

\[
R = \frac{P_a - P_v}{ERBF} \times 1328,
\]
RENAL RESPONSE TO HYPERTONIC SALINE

where \( P_a \) = mean arterial blood pressure in mm Hg, \( P_v \) = mean renal venous pressure (assumed to be 10 mm Hg) and \( \text{ERBF} = \) estimated renal blood flow in ml/sec/1.73 m². Osmolar and free water clearances (\( C \)) were calculated in the manner described by Smith. 21

The fraction of filtered sodium (\( Na^+ \)) which was not reabsorbed by the renal tubules (\( E/F_{Na^+} \)) was calculated by dividing excreted sodium (\( U_{Na^+}V \)) by filtered sodium (\( C_{INPNa} \)) and was expressed as a percentage: \( E/F\% \) for potassium (\( K^+ \)), chloride (\( Cl^- \)), urate (\( Ur \)), calcium (\( Ca \)), and magnesium (\( Mg \)) were calculated similarly. To make both the latter calculations, it was assumed that 60% of the total plasma Ca concentration and 70% of the total plasma Mg concentration underwent ultrafiltration at the glomerulus. 22, 23

Results are reported in the text as mean and standard deviation (\( \pm s \)). Differences between means of values obtained in the same subjects during the same clearance study were compared utilizing the Student \( t \)-test for paired variables; differences between means of values obtained in different studies were compared by the Student \( t \)-test for unpaired variables. A change or difference was termed significant if the value of \( P \) was < 0.01. Regression lines and correlation coefficients were calculated according to standard statistical technics. 24

Results

The results of measurements performed during control clearance periods and during that clearance period in each of the 24 studies in which urinary sodium excretion reached its highest value in response to 2.5% saline infusion appear in tables 1 through 3. Various derived relationships are presented in table 4 and in figures 1 and 2.

Renal Hemodynamics

Although renal hemodynamics during control periods were significantly different in the normotensive and hypertensive subjects (tables 1-4), the mean changes in glomerular filtration rate, renal plasma flow, and sodium excretion induced by 2.5% saline infusions in the two types of patients comprising the study group did not differ significantly. Mean arterial blood pressure did not rise in response to the hypertonic infusion (\( \Delta BP = 3 \pm 2 \)). Glomerular filtration rate increased, however, by 18 \( \pm 17 \) ml/min; RPF also increased by 173 \( \pm 24 \) ml/min and ERBF rose by 237 \( \pm 34 \) ml/min. The filtration fraction fell by 0.03 and renal vascular resistance declined 3567 \( \pm 589 \) dynes sec cm⁻².

Plasma Electrolytes

During control periods the mean plasma electrolyte concentrations, urate levels, and osmolality found in the normotensive subjects did not differ significantly from those of the hypertensive patients. In response to infusions of 2.5% NaCl, plasma sodium and chloride concentrations increased along with the osmolality (table 3). The mean potassium concentration increased slightly, and there were modest reductions of the concentrations of calcium, magnesium, and urate.

Urinary Electrolyte Excretion

In response to the hypertonic saline infusions, the urinary excretion rates of six ions rose significantly (tables 1 and 2). Mean sodium excretion increased from 162 \( \mu \)Eq/min during control periods to peak values averaging 2487 \( \mu \)Eq/min. Simultaneously, chloride output increased from 114 to 3375 \( \mu \)Eq/min, and potassium excretion rose from 51 to 135 \( \mu \)Eq/min; calcium excretion increased from 121 to 622 \( \mu \)g/min and magnesium output increased from 87 to 252 \( \mu \)g/min. The urinary excretion rate of urate also rose significantly in response to the 2.5% saline infusions from an average value of 544 \( \mu \)g/min during control periods to 880 \( \mu \)g/min at peak natriuresis. Although glomerular filtration increased during the infusions, electrolyte excretion increased to a greater extent so that the excretion rate of each ion per milliliter of glomerular filtrate was significantly higher at peak natriuresis than during control periods.

Solute and Free Water Clearance

Mean urinary osmolality, total solute excre-
Table 1

Clearance Data from 24 Studies: Normotensive Subjects

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Glomerular filtration rate (CrCl) (ml/min)</th>
<th>Renal blood flow (Cfip/1-Hct) (ml/min)</th>
<th>Filtration fraction</th>
<th>Renal vascular resistance (dynes sec cm⁻⁵)</th>
<th>Osmolar clearance (C₉₆₀⁺⁺) (ml/min)</th>
<th>Free water clearance (C₅₀⁻⁻) (ml/min)</th>
<th>Urinary ion excretion</th>
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<td>GG</td>
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<td>95</td>
<td>158</td>
<td>0.19</td>
<td>4531</td>
<td>4.1</td>
<td>11.5</td>
<td>195 47 98 165 78 1070</td>
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<td>97</td>
<td>95</td>
<td>0.23</td>
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<td>11.6</td>
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<td>DN</td>
<td>3</td>
<td>100</td>
<td>119</td>
<td>0.16</td>
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*Average values obtained during control period.
† Average values obtained during clearance period after 2.5% saline administration in which urinary sodium excretion reached a maximum.
### Hypertensive Subjects

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<th>Patient</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Glomerular filtration rate (CrCl) (ml/min)</th>
<th>Renal blood flow (CrCl:1.17et) (ml/min)</th>
<th>Filtration fraction</th>
<th>Renal vascular resistance (dynes sec cm⁻⁵)</th>
<th>Osmolar clearance (C₀,osm) (ml/min)</th>
<th>Free water clearance (C₀,l) (ml/min)</th>
<th>Urinary ion excretion</th>
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Table 2
Table 3

Plasma Electrolyte Changes*

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<th>Control</th>
<th>At peak natriuresis</th>
<th>Difference ± SED</th>
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<tr>
<td>Na (mEq/L)</td>
<td>137</td>
<td>149</td>
<td>12 ± 1†</td>
</tr>
<tr>
<td>Cl (mEq/L)</td>
<td>104</td>
<td>119</td>
<td>15 ± 1†</td>
</tr>
<tr>
<td>K (mEq/L)</td>
<td>3.5</td>
<td>3.8</td>
<td>0.3 ± 0.1‡</td>
</tr>
<tr>
<td>Ca (mg%)</td>
<td>8.92</td>
<td>8.08</td>
<td>0.84 ± 0.17†</td>
</tr>
<tr>
<td>Mg (mg%)</td>
<td>1.98</td>
<td>1.90</td>
<td>0.09 ± 0.04‡</td>
</tr>
<tr>
<td>Urate (mg%)</td>
<td>5.36</td>
<td>4.74</td>
<td>0.62 ± 0.06†</td>
</tr>
</tbody>
</table>

*The values obtained in all studies during control periods and during the clearance period of maximal natriuresis have been averaged.

† P < 0.01.
‡ P < 0.02.

Excretion and osmolar clearance also rose significantly in all studies (tables 1 and 2). Although there were no differences in urinary concentration between normotensive and hypertensive subjects during the control periods, the urine of hypertensive patients was less concentrated than that of normotensive subjects during clearance periods of greatest salt excretion. At peak natriuresis in the normotensive subjects $U_{\text{osm}}$ was $445 ± 118$ mOsm/kg of $H_2O$ and $U_{Na}$ was $187 ± 30$ mEq/L, while in the hypertensives, $U_{\text{osm}}$ was $345 ± 92$ mOsm/kg of $H_2O$ and $U_{Na}$ was $155 ± 22$ mEq/L. $Tc_{H_2O}$ averaged $4.0 ± 1.5$ ml/min in the normotensive subjects and $1.8 ± 2.1$ ml/min in the hypertensives (difference significant at $P < 0.02$).

Fractional Excretion

In figure 1 are depicted the changes in the excretion fraction of each ion which were induced by hypertonic saline infusions. The fraction of filtered sodium which appeared in the urine increased from 1.4% during control periods to 14.5% at peak natriuresis; the excretion fraction of chloride increased from 1.2 to 18.9%. Fractional excretion of calcium increased from 2.7 to 12.8% while $E/F$ magnesium rose from 7.3% to 19.1%. The fraction of filtered urate which appeared in the urine also rose significantly from 12.5 to 18.7% during the 2.5% saline infusions.

![Figure 1](image-url)

The effect of 2.5% NaCl infusions upon the fraction excretion rate of six ions.

Circulation, Volume XLI, January 1970
Figure 2
(A) Relationship between $E/F_C\%$ and $E/F_Na\%$ in control periods (open symbols) and during clearance periods of peak natriuresis after hypertonic saline administration (dark symbols). Normotensives are identified by circles, hypertensives by triangles. A significant direct correlation is seen. (B) Relationship between $E/F_Mg\%$ and $E/F_Na\%$ in control periods in the clearance period of peak natriuresis. (C) Relationship between $E/F_CO\%$ and $E/F_Na\%$. (D) Relationship between $E/F_K\%$ and $E/F_Na\%$.

Relationships Between Fractional Excretion Rates of Sodium, Urate, and Other Ions

The fraction of filtered sodium which escaped tubular reabsorption ($E/F_{Na}\%$) has been plotted in figure 2 against the corresponding excretion fraction ($E/F\%$) of Ca,
Table 4

Relationships Between Changes in Sodium Transport Induced by 2.5% Saline Infusions and Simultaneous Alterations in Net Fractional Reabsorption of Other Ions

<table>
<thead>
<tr>
<th>Data*</th>
<th>No. periods</th>
<th>Correl. coefficient‡</th>
<th>Slope</th>
<th>Intercept</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta T_{Ca}$ vs $\Delta T_{Na}$</td>
<td>103</td>
<td>0.856</td>
<td>0.986</td>
<td>-1.373</td>
<td>3.596</td>
</tr>
<tr>
<td>$\Delta T_{Mg}$ vs $\Delta T_{Na}$</td>
<td>103</td>
<td>0.741</td>
<td>0.541</td>
<td>-2.882</td>
<td>4.672</td>
</tr>
<tr>
<td>$\Delta T_{Cl}$ vs $\Delta T_{Na}$</td>
<td>119</td>
<td>0.985</td>
<td>0.788</td>
<td>0.153</td>
<td>1.157</td>
</tr>
<tr>
<td>$\Delta T_{K}$ vs $\Delta T_{Na}$</td>
<td>119</td>
<td>0.782</td>
<td>0.304</td>
<td>-3.597</td>
<td>4.202</td>
</tr>
<tr>
<td>$\Delta T_{Ur}$ vs $\Delta T_{Na}$</td>
<td>96</td>
<td>0.731</td>
<td>0.741</td>
<td>-4.042</td>
<td>4.723</td>
</tr>
</tbody>
</table>

* $T$ calculated as $\frac{Tx}{F_{x(c)}} - \frac{Tx}{F_{x(e)}}$, where $F_x = \frac{F_{x(c)}}{c}$ and $T_x = \frac{F_{x(c)}}{x} - \frac{F_{x(e)}}{e}$ - urinary excretion rate.

‡ Significant at $P < 0.01$.

Figure 3

The change in $E/F_{Na}\%$ induced by 2.5% saline administration has been plotted against simultaneous changes in $E/F_{Na}\%$ in normotensives (●) and hypertensives (▲). All values are depicted except those for 39 periods immediately after saline infusions were begun. The values were omitted because in the early periods induced changes in excretion rate of both ions were very small and clustered at the lower left corner of the graph. A direct relationship between induced alterations in sodium and net urate reabsorption is apparent.

Mg, Cl, and urate for the mean of control periods and for the period of peak sodium excretion in each study. Fractional sodium excretion was significantly related to the fractional excretion of calcium, magnesium, potassium, chloride, and urate.

The change from control in the net fractional reabsorption of each of the ions has been calculated for every clearance period after hypertonic saline administration. In figure 3 the changes in $E/F_{Na}\%$ are plotted against concurrent changes in $E/F_{Ur}\%$; and in
Table 4 the depression of net fractional sodium reabsorption in each period has been related to the simultaneous changes from control in net tubular reabsorption of the other ions. Depressed fractional sodium reabsorption during hypertonic saline infusion was significantly ($P < 0.01$) related to simultaneous decreases in net fractional reabsorption of Ca ($r = 0.856$), Mg ($r = 0.741$), K ($r = 0.782$), Cl ($r = 0.985$), and urate ($r = 0.731$).

**Discussion**

In the present studies increased urinary excretion and decreased net fractional renal tubular reabsorption of sodium, chloride, potassium, calcium, magnesium, and urate were observed in response to infusions of hypertonic saline in a group of normotensive and hypertensive subjects. The impairment of net fractional reabsorption of each of the ions during the infusions was directly related to the simultaneous impairment of fractional sodium reabsorption and was accompanied by significant increases in glomerular filtration and renal plasma flow.

The significant elevations of the fraction of filtered sodium excreted by the subjects in response to 2.5% saline is similar to that found during infusions of isotonic saline in normotensive subjects by Crawford and Ludemann and in hypertensive patients by a number of investigators. Studies documenting a relationship between sodium and urate excretion rates during saline infusions in man have not previously been published. A relationship between the tubular transport of the two ions has been implied, however, from observations: (1) that hyperuricemia and diminished urate excretion accompanied reduced sodium output in patients who received low sodium diets or diuretics and (2) that the excretion rates of urate and of sodium per milliliter of glomerular filtrate increased together in advanced uremia. Augmented rates of calcium and magnesium excretion with a relationship to sodium excretion like those in the present studies have been observed during saline infusions in the dog and during osmotic diuresis induced by hypertonic-saline-urea in five normal subjects studied by Better et al.

Although fractional reabsorption of sodium and of five other ions declined during 2.5% saline infusions in the present studies, an absolute reduction of the rate of tubular electrolyte transport was not documented because the rises in glomerular filtration rate which occurred during the infusions increased the filtered load of each ion. It has been shown in the dog, however, that isolated increases in GFR are not necessarily accompanied by depression of fractional sodium reabsorption and that expansion of the extracellular fluid volume by isotonic or hypertonic saline infusions may augment the urinary excretion rates of sodium, chloride, calcium, and magnesium even when glomerular filtration and the filtered load of each ion are reduced below control values.

According to current concepts, urate is filtered at the glomerulus, completely reabsorbed, and secreted by the renal tubules in proximal and possibly distal portions of the nephron. Whether the increased fractional excretion rate of urate observed in response to 2.5% saline resulted from increased tubular secretion or diminished reabsorption cannot be directly assessed in the present studies. However, the close correlation between depressed net urate reabsorption and depressed sodium reabsorption in individual patients and among the entire group of subjects suggests that the rise in urate output resulted from impaired tubular reabsorption of this ion. This interpretation is consistent with the preliminary report by Steele who found increased urate excretion during saline infusions in normal subjects who had been pretreated with pyrazinamide to block urate secretion. The predominant site of diminished urate reabsorption during saline infusions is probably the proximal tubules because (1) the bulk of urate reabsorption occurs in this nephron segment and (2) transport of three ions which were excreted with urate, (Na, Mg, Ca) is depressed in proximal tubules during ECF volume expansion.
The mechanisms which determine the natriuretic response to expansion of the ECF volume by saline infusions have not been completely defined. Current explanations suggest that depressed fractional sodium reabsorption may result from altered intrarenal hemodynamics or from the operation of a humoral factor other than aldosterone or both. Although the present studies were not designed to evaluate these mechanisms, the lack of specificity of the excretory response to 2.5% saline infusion has implications for both theories.

Experiments by Martino and Earley,4, 36, 37 Lewy and Windhager,38 and of Koch and associates39 have indicated that increased hydrostatic pressure or diminished colloid osmotic pressure in peritubular capillaries is associated with an increased interstitial pressure within the kidneys (increased wedged renal venous pressure)40 and with depressed net reabsorption of sodium in proximal tubules. The increases in renal blood flow which were consistently observed during the 2.5% saline infusions in the present studies are qualitatively similar to those which were associated with significant rises in renal interstitial pressure in normal and hypertensive subjects studied by Lowenstein and associates.41 The multiplicity of ions (Na, K, Cl, Ca, Mg, and urate) excreted in response to the infusions suggests that depressed uptake of sodium and water by peritubular capillaries may retard the net reabsorption of a variety of other ions whose transport is electrogenically coupled to that of sodium or which are reabsorbed by concentration-dependent processes which thus would be influenced by alterations in the rate of tubular water reabsorption.42 If medullary vasodilatation also occurred during the infusions and allowed transmission of an elevated arterial pressure to the vasa recta, the resulting reduction in the rate of net sodium reabsorption in the loop of Henle might explain the reduced $U_{\text{osm}}$ and $T_{\text{H}_{2}\text{O}}$ observed in the hypertensive subjects during the infusions, a finding similar to that recently reported by Buckalew et al.10 during isotonic saline infusions.

Alternatively, if a natriuretic hormone was responsible for depressed fractional sodium reabsorption in the present experiments, the data suggest that such a postulated factor may act to inhibit sodium transport at a site common to reabsorption of several other ions, or that it induces a generalized depression of tubular reabsorptive capacity. Several natriuretic factors have been found after ECF volume expansion in animals and in normal and hypertensive patients by different groups of investigators.43-46 The recent reports by Bricker and associates44, 47 of a dialyzable substance in the plasma of saline-loaded dogs and uremic patients which inhibits para-aminohippurate uptake by renal cortical slices and reduces short-circuit current in the frog skin preparation is also consistent with the hypothesis of a relatively nonselective depression of tubular function by the postulated hormone.

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