Renal response to graded intravenous hypertonic NaCl infusion in healthy and hypertensive subjects:dose-related impairment in distal NaCl reabsorption*

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Enhanced sodium excretion after a salt load has been described as "exaggerated natriuresis" (EN) in patients with various forms of hypertension.[1-4] Its mechanisms and the renal site of impaired sodium reabsorption have been extensively investigated, but are increasingly controversial in the recent literature. A primary tubular defect or an abnormal response to volume expansion were considered as possibly responsible for the phenomenon[9, 11] and a predominant role was claimed for both the proximal tubules[5-8] and the distal nephron.[9-11] The abnormal renal handling of sodium previously was thought to be characteristic to all patients with essential hypertension, but very recently it was postulated as a feature of renin suppression.[12-14] Our preliminary studies suggested that depression of free water reabsorption ($T^c_{H_2O}$) was a more sensitive indicator of the altered renal response to acute NaCl loading than EN itself, becoming more pronounced with increasing the load. Furthermore, a similar tendency was found also in the healthy persons when very high NaCl loads were used. Therefore, the present work was designed to compare the renal responses of healthy subjects and "normal renin" essential hypertensive patients to graded acute intravenous hypertonic NaCl loading with special reference to changes in the normal relationship between solute excretion ("osmolal clearance," Cosm) and $T^c_{H_2O}$. From such a comparison we expected to exclude an intrinsic tubular abnormality and to demonstrate that EN is an acute renal response abnormally reset to a lower level in the hypertensive patients.

Materials and methods

Participants. Studies were performed on 12 patients with uncomplicated essential hypertension (average age: 34.3 ± 2.9 (SEM) years) and on 15 healthy volunteers (average age: 23.5 ± 1.9 years). In the Protocol I and II studies (see below) six male and two female healthy subjects and 10 male and two female hypertensive patients participated; Protocol III was performed on four male and three female healthy persons. In the hypertensive groups the elevation of blood pressure was from mild to moderate and all patients were free from any demonstrable cardiovascular, renal, or endocrinological consequences of long-standing hypertension. Normal renal function was assessed by urine analysis, creatinine clearance, and DDAVP* concentration test.[15] Renovascular hypertension was ruled out by normal radiorenogram, intravenous pyelogram and in certain cases by renal arteriogram. Other forms of secondary hypertension were excluded by appropriate tests including renal biopsy. Hypertensive

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*1-Desamino-8-D-Arginine Vasopressin.

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Table 1. Effects of a "moderate" acute intravenous sodium load on the excretion of various ions in healthy subjects and in hypertensive patients

	$C_{Na} \times 100/GFR$ (%)		$C_K \times 100/GFR$ (%)		$C_{Ca} \times 100/GFR$ (%)		$C_{Mg} \times 100/GFR$ (%)		$C_P \times 100/GFR$ (%)		$C_{Cl} \times 100/GFR$ (%)	
	N_1	H_1	N_1	H_1	N_1	H_1	N_1	H_1	N_1	H_1	N_1	H_1
Baseline	1.75 ± 0.68	1.60 ± 0.36 °	15.85 ± 3.50	19.24 ± 1.90 °	4.20 ± 0.64	3.53 ± 0.52 °	5.10 ± 0.54	4.14 ± 0.86 °	10.72 ± 1.49	8.54 ± 1.48 °	2.73 ± 0.80	2.30 ± 0.41 °
During NaCl loading	4.56 ± 2.20	5.64 ± 1.08 °	14.09 ± 1.73	23.19 ± 2.26 ª	6.41 ± 1.87	6.98 ± 1.19 °	7.26 ± 2.04	6.98 ± 1.36 °	21.70 ± 3.21	18.10 ± 2.18 °	5.68 + 1.44	8.26 ± 1.59 °
After loading	4.78 ± 0.79	5.65 ± 0.73 °	23.79 ± 1.64	34.48 ± 2.57 ª	4.95 ± 0.94	4.85 ± 0.85 °	4.51 ± 0.47	3.97 ± 0.70 °	31.03 ± 3.18	29.07 ± 2.99 °	6.38 ± 1.13	9.06 ± 1.13 °
Maximal change	6.29 ± 2.12	7.61 ± 1.36 °	14.10 ± 3.97	20.76 ± 3.03 °	4.04 ± 1.91	6.67 ± 1.33 °	3.64 ± 2.40	5.76 ± 1.39 °	23.65 ± 4.00	29.08 ± 3.48 °	5.57 ± 0.90	14.01 ± 2.62 ª
p <	0.05	0.001	0.05	0.001	NS	0.005	NS	0.01	0.01	0.001	0.05	0.01

N_1 = healthy subjects (n = 4); H_1 = hypertensive patients (n = 9); ° = not significant; ª = $p < 0.05$ (hypertensive vs normal).
"Moderate" NaCl load = intravenous infusion of 2.92% NaCl during 60 minutes. During NaCl loading = mean of periods 2 to 6.
After loading = mean of periods 7 to 10. Maximal change = mean of individual maximum (in a single period from 3 to 10) minus baseline.
Data are presented as mean ± SEM.

patients with abnormal (low or high) plasma renin activity values[17] were excluded from the study. A part of the study (Protocol I) was carried out in the University Hospital, Utrecht, The Netherlands and the other part (Protocols II and III) in the János Hospital, Budapest, Hungary. The investigations were carried out according to the Declaration of Helsinki. The nature of the investigation was fully explained to each person and written consent was obtained from them. All antihypertensive treatments were discontinued 1 month before the study. All participants (except three hypertensive patients) were placed on a diet containing 200 mEq. Na per day, for 4 to 7 days before the study. In three members of the hypertensive group H_2 (see below) the daily Na intake was 150 mEq.

Protocols.

Protocol I. "Moderate" NaCl loading in four healthy subjects (group N_1) and in nine hypertensive patients (group H_1). Two days before the study 40 μg DDAVP (Minirin, Ferring AB, Malmö, Sweden) was given intranasally (20 μg into each nostril) three times a day. On the day of the study of 7 A.M. and 11 A.M. 40-40 μg DDAVP were given intranasally. The study began after an overnight fast and water deprivation at 9 A.M. After two 30 minute control clearance periods ("baseline study") 1 liter 2.92% NaCl solution (500 mEq. Na) was infused during 60 minutes. During this period and in the next hour altogether six 20 minute clearance periods were run. The study was concluded by two 30 minute periods. Altogether 10 periods were done during 4 hours.

Protocol II/a. "High" NaCl loading by rapid infusion in four healthy subjects (group N_2). The procedure was the same as in Protocol I except: 2 liters 2.92% NaCl (1,000 mEq. Na) were infused during 60 minutes; an intravenous dose of 4 μg DDAVP was given at 9 A.M. in addition to the two intranasal doses given at 7 A.M. and 11 A.M.

Protocol II/b. "High" NaCl loading by rapid infusion in three hypertensive patients (group H_2). The procedure was the same as in Protocol I except: 1½ liters 2.92% NaCl were infused during 80 minutes.

Protocol III. "High" NaCl loading by slow infusion in seven healthy subjects (group N_3). Prepatatory DDAVP treatment was not given, but during the whole experiment 500 mU. lysine-vasopression per hour were infused intravenously. No baseline periods were run. One liter 2.5% NaCl was infused intravenously during the first two hours and 500 ml. 5% NaCl was infused during the second two hours. Altogether, 854 mEq. Na were given. During the last hour one 60 minute clearance period was performed.

Urine was collected by an indwelling catheter. Blood samples were taken through an indwelling venous catheter (Butterfly, Abbott) in periods 1,2,5,7, and 9 of Protocols I,II/a and II/b and at midpoint of the clearance period of Protocol III.

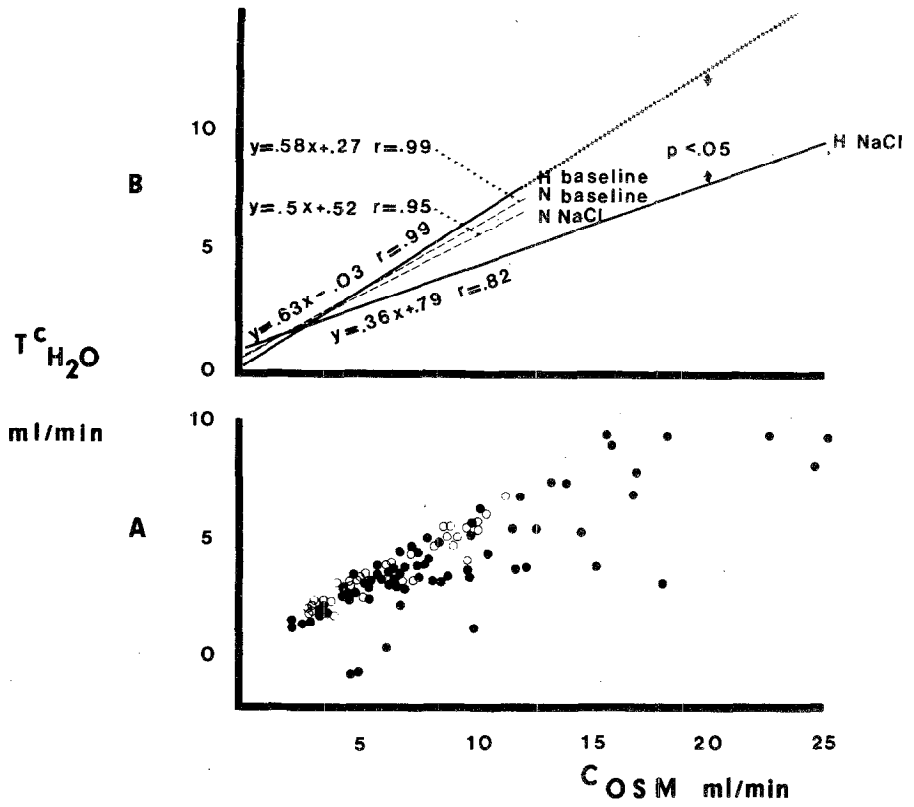

Fig. 1. Relationship between Cosm and $T^c_{H_2O}$ under the influence of a "moderate" intravenous NaCl load in healthy *(circles; N)* and in hypertensive *(black dots; H)* subjects. *A*, All $T^c_{H_2O}$ values obtained during and after intravenous NaCl loading were plotted against Cosm. *B*, Regression lines of data of baseline and NaCl studies. Note the significant difference between the slopes in the hypertensive group *(solid line, baseline extrapolated)* vs. no difference in the healthy group *(dashed line)*. *Asterisk* = $p < 0.05$.

Urine and blood samples were analyzed for creatinine, sodium, potassium (in all groups), calcium, magnesium, phosphate (in all but group N_3), and for uric acid (only in groups N_1 and N_2) by procedures applied to the Technicon-Autoanalyzer. Chloride was measured by a chloridometer. All ion clearances were expressed as a percentage of GFR (creatinine clearance). When calculating Ca and Mg clearances, it was assumed[16] that 60% of the total plasma Ca concentration and 70% of the total Mg concentration underwent ultrafiltration in the glomerulus. Osmolality was determined by an Advanced Osmometer; Cosm and $T^c_{H_2O}$ were calculated according to standard formulas. In order to save space in the Tables, contracted data of periods 1 and 2 ("baseline") 3 to 6 ("during NaCl loading") and 7 to 10 ("after loading") are included. For unity, period 6 was included in the "during NaCl loading" contracted data of Protocols I and II/a. Correlation coefficients and regression lines were computed by the method of least squares. Statistical significance was determined by the paired t test except when different groups were compared; then the unpaired t test was used. Data are presented as mean ± SEM.

Results

Baseline relationship between Cosm and $T^c_{H_2O}$. A "normal" relationship between Cosm and $T^c_{H_2O}$ was established during high NaCl intake by including all baseline values of the healthy subjects (groups N_1 and N_2) and hypertensive patients (groups H_1 and H_2). The relationship is expressed by the formula $y = 0.58 \times +0.27$ ($r = 0.99$; $p < 0.001$) in the healthy subjects and by $y = 0.63 \times -0.03$ ($r = 0.99$; $p < 0.001$) in the hypertensive patients. No statistical difference was found between the slopes (Fig. 1).

Effect of a "moderate" intravenous NaCl load on the baseline relationship between Cosm and $T^c_{H_2O}$

Healthy subjects (group N_1). The time-course of changes in Cosm and $T^c_{H_2O}$ can be seen in Fig. 2.

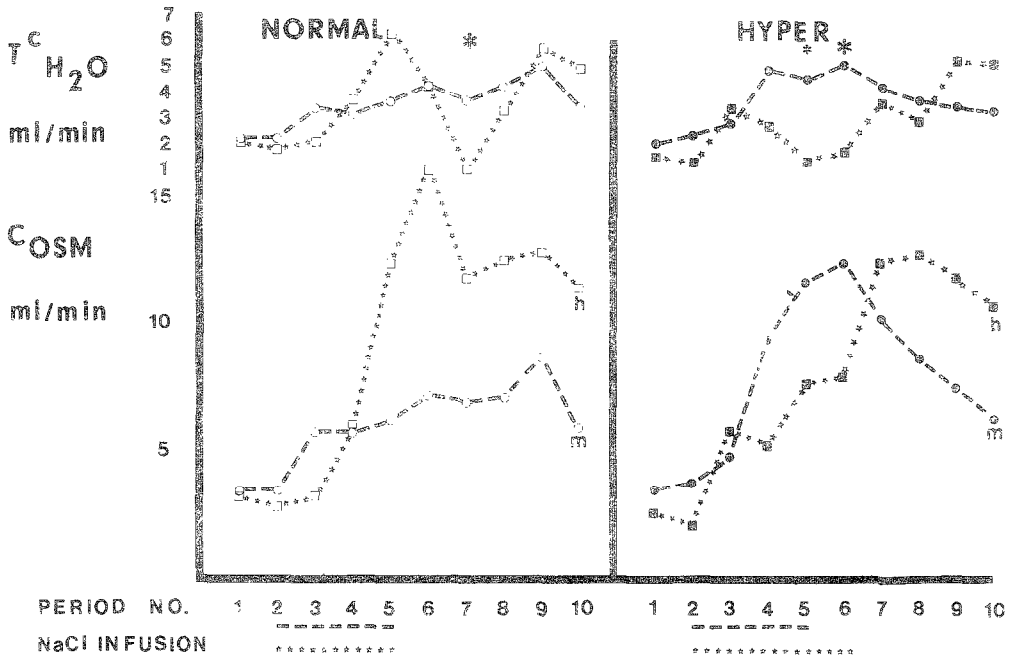

Fig. 2. Time course of changes in solute excretion *(Cosm)* and free water reabsorption ($T^c_{H_2O}$) during and after acute intravenous NaCl loading in normal subjects and in hypertensive patients. Note the transitory decrease in $T^c_{H_2O}$ after a high NaCl load *(h)* apparently not related to changes in Cosm in both groups. "Moderate" NaCl load *(m)* induced expected changes.

Table II. Effects of graded acute intravenous sodium loading on the excretion of various ions in healthy subjects

	$C_{Na} \times 100/GFR$ (%)		$C_K \times 100/GFR$ (%)		$C_{Ca} \times 100/GFR$ (%)		$C_{Mg} \times 100/GFR$ (%)		$C_{Cl} \times 100/GFR$ (%)		$C_P \times 100/GFR$ (%)	
	N_1	N_2	N_1	N_2	N_1	N_2	N_1	N_2	N_1	N_2	N_1	N_2
Baseline	1.75 ± 0.68	1.03 ± ° 0.18	15.85 ± 3.50	19.05 ± ° 4.21	4.20 ± 0.64	3.55 ± ° 0.79	5.10 ± 0.54	4.56 ± ° 0.26	13.32 ± 2.73	10.23 ± ° 0.64	10.72 ± 1.49	6.98 ± [b] 0.59
During NaCl loading	4.56 ± 2.20	6.08 ± ° 1.04	14.09 ± 1.73	20.66 ± [b] 2.66	6.41 ± 1.87	9.22 ± ° 2.30	7.26 ± 2.04	11.89 ± [a] 0.89	11.23 ± 1.56	11.08 ± ° 1.13	21.70 ± 2.21	18.65 ± ° 3.95
After loading	4.78 ± 0.79	10.42 ± [c] 1.35	23.79 ± 1.64	48.66 ± [c] 2.58	4.95 ± 0.94	10.42 ± [c] 1.53	4.51 ± 0.47	9.03 ± [c] 0.68	11.17 ± 1.80	14.58 ± ° 1.69	31.03 ± 3.18	36.17 ± ° 6.49
Maximal change	6.29 ± 2.12	13.81 ± [a] 2.85	14.10 ± 3.97	39.84 ± [b] 4.47	4.04 ± 1.91	15.81 ± [b] 2.99	3.64 ± 2.40	12.81 ± [b] 1.53	−3.30 ± 1.33	6.36 ± [b] 1.14	23.65 ± 4.00	25.47 ± [c] 11.47
p <	0.05	0.05	0.01	0.001	NS	0.005	NS	0.001	0.05	0.02	0.001	0.05

N_1 = four healthy subjects, 1 liter 2.92% NaCl during 1 hour; N_2 = four healthy subjects, 2 liters 2.92% NaCl during 1 hour; ° = not significant
[a] = $p < 0.05$; [b] = $p < 0.01$; [c] = $p < 0.001$.

There was a parallel rise in both parameters up to period 9 during and after NaCl infusion. The relationship is expressed by the formula $y = 0.50 \times + 0.52$ ($r = 0.95$; $p < 0.001$) (Fig. 1). The slope of this line was not significantly different from that of the baseline relationship. The relationship between Cosm and $T^c_{H_2O}$ remained constant when Cosm was increased either by prolonged high Na intake or by acute intravenous NaCl loading.

Hypertensive patients (group H_1). The relationship between Cosm and $T^c_{H_2O}$ is expressed by the formula $y = 0.36 \times + 0.79$ ($r = 0.82$; $p < 0.001$). The slope of this line was significantly different from that of the baseline relationship ($p < 0.05$; Fig. 1). Fractional Cl and K excretion increased to

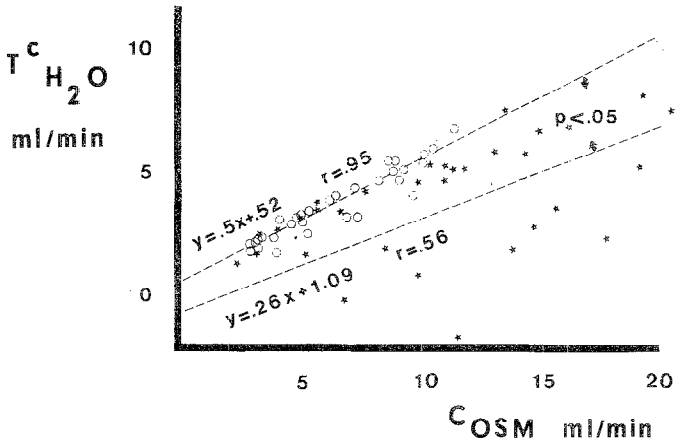

Fig. 3. Relationship between Cosm and $T^c_{H_2O}$ in healthy subjects under the influence of "moderate" NaCl loading *(group N_1; circles)* and "high" NaCl loading *(group N_2; black stars).*

a significantly higher level in this group than in group N_1, but there was no significant difference in Na, Ca, Mg, and P excretion between the groups (Table I).

Effect of high intravenous NaCl loads on the relationship between Cosm and $T^c_{H_2O}$ established during "moderate" NaCl loading.

Healthy subjects (group N_2, Protocol II/a). The relationship during high NaCl loading is expressed by the formula $y = 0.26 \times + 1.09$ ($r = 0.56$; $p < 0.001$). The slope of this line was significantly different from that of moderate loading ($p < 0.05$). The correlation between Cosm and $T^c_{H_2O}$ became much less close after a high NaCl load than after a moderate load (Figs. 2 and 3). There was a significant difference ($p < 0.001$) between the mean maximum and minimum $T^c_{H_2O}$ values (6.74 ± 0.48 ml./minute vs 1.42 ± 0.61 ml./minute) obtained during high NaCl loading, but without a significant difference between the corresponding mean Cosm values (15.17 ± 1.24 ml./minute vs 11.92 ± 1.57 ml./minute), suggesting that the rise of Cosm per se was not responsible for the dramatic decrease in $T^c_{H_2O}$ (Fig. 2). The rises in fractional Na, K, Ca, Mg, and Cl excretions were significantly higher after high NaCl loading than after moderate NaCl loading (Table II; Fig. 4), but there was no significant difference in P excretions. It is interesting that fractional uric acid excretion slightly decreased after moderate NaCl loading, but significantly increased in response to a high NaCl load.

It should be noted that during administration of a relatively high dose of NaCl by *slow* intravenous infusion *(group N_3, Protocol III),* the correlation between changes of Cosm and $T^c_{H_2O}$ remained excellent, $r = 0.99$; $p < 0.001$).

Hypertensive patients (group H_2, Protocol II/b). The relationship between Cosm and $T^c_{H_2O}$ (expressed by the formula $y = 0.27 \times + 0.59$) was less close after high loading ($r = 0.49$; $p < 0.05$) than after a moderate load in group H_1 ($r = 0.82$; $p < 0.001$). There was a significant difference ($p < 0.001$) between the mean maximum and minimum $T^c_{H_2O}$ values (5.87 ± 0.43 ml./minute vs 0.86 ± 0.59 ml./minute), but no significant difference was found in the corresponding mean Cosm values (11.09 ± 1.42 ml./minute vs 7.92 ± 1.81 ml./minute).

Discussion

This study clearly shows that acute NaCl loading may depress $T^c_{H_2O}$ not only in hypertensive patients,[9, 10] but also in healthy subjects (Figs. 1 to 3). In earlier studies carried out in dehydrated healthy subjects, this has not been reported, because during intravenous administration of hypertonic NaCl solutions there was no evidence for an upper limit of $T^c_{H_2O}$, as the increasing delivery from the proximal nephron enhanced NaCl transport out of the ascending limb of Henle's loop.[18] However, in the previous studies only moderate NaCl doses were used,[18] and the present results show that depression of $T^c_{H_2O}$ occurred apparently as a dose-related consequence of acute NaCl loading. The augmentation of $T^c_{H_2O}$ at any rate of distal delivery of NaCl was significantly less during high NaCl loading than after moderate NaCl loading, suggesting impaired

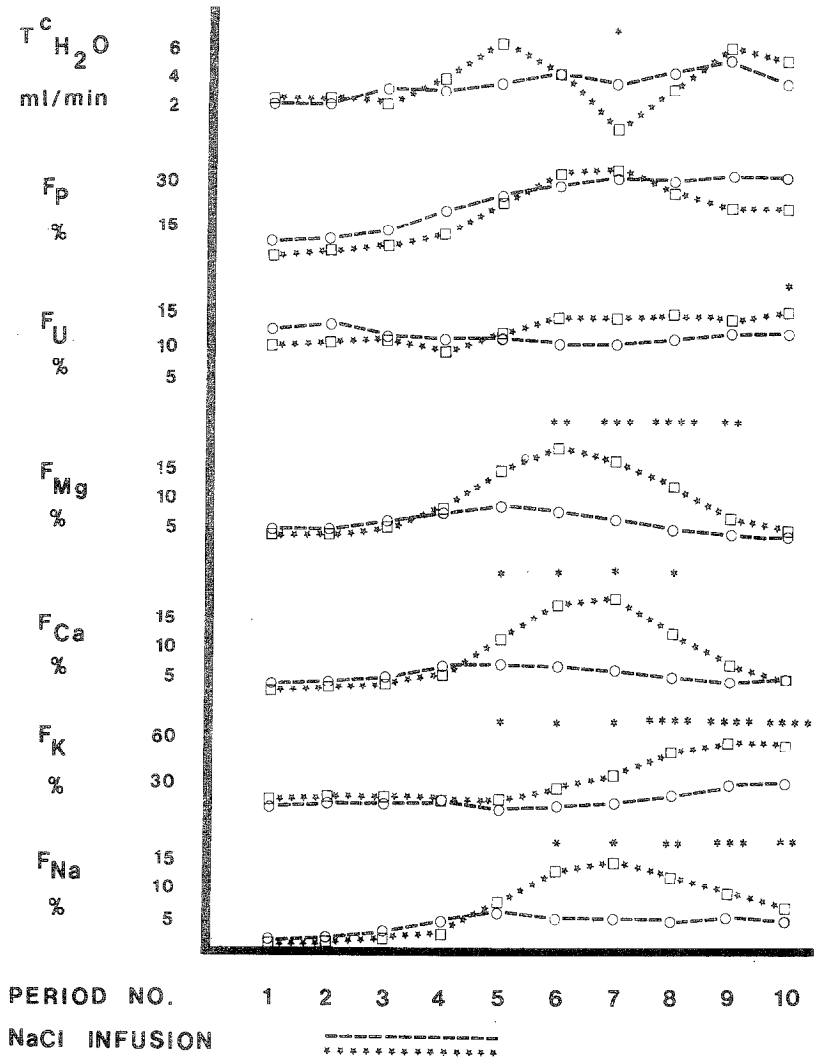

Fig. 4. Time course of changes in fractional excretion of Na, K, Ca, Mg, uric acid *(U)* and phosphate *(P)* as well as in $T^c_{H_2O}$ during and after "moderate" NaCl loading *(circles)* and "high" NaCl loading *(squares)*. *$p < 0.005$; **$p < 0.01$; ***$p < 0.005$; ****$p < 0.001$.

NaCl reabsorption in Henle's loop. Our most striking finding was the disruption of the normal correlation between Cosm and $T^c_{H_2O}$, with sometimes positive free water clearance values when healthy subjects were infused with high intravenous NaCl loads. Our results are in agreement with those obtained in other studies of the hydrated dog[21] and of human subjects,[20, 22] suggesting that volume expansion inhibits fractional NaCl reabsorption in the distal nephron in a dose-related fashion. Depression of the fractional NaCl reabsorption in the distal nephron obviously played a definitive role in the "exaggeration" of natriuresis when high NaCl loads were given to healthy subjects. The peak fractional Na, Ca, and Mg excretions were simultaneous with the decrease in $T^c_{H_2O}$ (Fig. 4), also supporting the hypothesis that the reabsorption of interrelated ions[16] was inhibited in the distal nephron. If fractional phosphate excretion is (within limitations[7]) an acceptable "proximal marker,"[19] then the lack of difference in phosphaturia between the moderate and high NaCl groups seems to support the distal interpretation (Table II).

An alternative explanation for the observed depression of $T^c_{H_2O}$ would be insufficient osmotic equilibration in the collecting tubules as a result of excessive osmotic diuresis or/and submaximal ADH effect. This, however, probably was not the case because osmotic diuresis (Cosm) was not

higher when the lowest $T^c_{H_2O}$ values were measured than in the presence of the maximal $T^c_{H_2O}$ values, and special care was taken to provide the subjects with supramaximal amounts of DDAVP[15] before and during the experiment. The persistence of the close correlation between Cosm and $T^c_{H_2O}$ in group N_3 (given not much less NaCl but in slow intravenous infusion) underlined the significance of the speed of acute loading in disruption of the normal relationship.

Our study confirmed that impaired NaCl transport in Henle's loop is a normal renal response to a certain degree of volume expansion.[20] In hypertensive persons this response is found even after relatively small NaCl loadings which do not cause any distortion in the normal relationship between Cosm and $T^c_{H_2O}$ in the healthy subject. Therefore EN in the hypertensives seems not to be due to an intrinsic renal tubular defect but is probably the consequence of a basically normal renal response reset to a lower level.

It was concluded that: (1) impaired distal NaCl reabsorption may also occur in response to acute NaCl loadings in the dehydrated healthy subject, and (2) EN is a normal renal response abnormally reset to a lower level in the hypertensive patient.

Summary

The effects of graded acute intravenous hypertonic NaCl loads on the baseline relationship between osmolal clearance and free water reabsorption established during high NaCl dietary intake and on the fractional excretion of various ions were investigated in 15 healthy subjects and in 12 "normal renin" essential hypertensive patients. No significant influence on the baseline relationship could be demonstrated after a *moderate* NaCl load in the healthy subjects, while free water reabsorption was depressed by the same intervention in the hypertensive patients. High NaCl loads induced depression of free water reabsorption in a dose-related fashion in both groups. No difference was found in phosphaturia between the groups after the same NaCl load as well as in the healthy persons after different NaCl loads, supporting the contention that the observed differences in free water reabsorption were not due to changes in the proximal nephron. It was concluded that: (1) impaired NaCl reabsorption in Henle's loop (depression of free water reabsorption) may also occur in response to acute NaCl loadings in healthy subjects, and (2) "exaggerated natriuresis" is the consequence of a normal renal response (imparied NaCl transport in Henle's loop) to a certain degree of volume expansion reset abnormally to a lower level in hypertensive patients.

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