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Moderate sodium restriction in hypertensive subjects: Renal effects of ACE-inhibition

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Moderate sodium restriction in hypertensive subjects: Renal effects of ACE-inhibition. It has been suggested that AII-mediated renal mechanisms limit the efficacy of moderate sodium restriction in the lowering of blood pressure (BP) in hypertension. We therefore studied renal hemodynamics and sodium handling in nine essential hypertensives in balance on 200 and on a 50 mmol sodium diet, before and during ACE-inhibition (enalapril 10 mg bid for 8 days) in a cross-over fashion. BP was similar on 50 and 200 mmol Na before enalapril, the fall in BP during enalapril was significantly more pronounced on 50 mmol Na. On 50 mmol Na, GFR and filtered Na were significantly lower, and tubular reabsorption was significantly higher than on 200 mmol Na. GFR increased during enalapril in 50 but not on 200 mmol Na. Consequently, the differences in GFR and filtered load elicited by sodium restriction were no longer present during ACE-inhibition. In contrast, the differences in tubular reabsorption between 50 and 200 mmol Na persisted during enalapril. In conclusion, moderate sodium restriction, not affecting BP, can elicit a renal hemodynamic response. As this response is blunted by ACE-inhibition it is probably mediated by AII. This blunting may contribute to the increased sodium sensitivity of BP during ACE-inhibition. The adaptation of tubular sodium reabsorption is not affected by ACE-inhibition.

The kidney plays a central role in the homeostatic response to sodium restriction [1]. When sodium intake is reduced to very low levels (<10 mmol Na daily), sodium excretion decreases exponentially and excretion matches intake again after three to five days [2]. The renal adaptation to this new state of sodium balance is characterized by decreases in glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), and a redistribution of renal blood flow [3, 4]. Studies in animals and in man have provided ample evidence that the renin–angiotensin–aldosterone–system (RAAS) mediates this response [5–7].

It has long been known that severe sodium restriction leads to a fall in blood pressure [8]. In antihypertensive treatment however, severe sodium restriction is impracticable and therefore, attention has been shifted to a more moderate restriction of dietary sodium [9]. Unfortunately, moderate sodium restriction lowers blood pressure only in a proportion of the patients thus treated.

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It has been suggested that above–mentioned RAAS-mediated renal adaptation limits the efficacy of sodium restriction in the lowering of blood pressure [10]. Yet the renal response to moderate sodium restriction in hypertensive man is not well–defined, and neither is the role of the RAAS in this response. We therefore studied renal hemodynamics and renal sodium handling in patients with essential hypertension on a moderately restricted and on a liberal sodium intake in a cross–over fashion. To assess the importance of the RAAS in the renal adaptive responses we repeated the studies after blocking the system by one week of treatment with the angiotensin I converting enzyme (ACE) inhibitor enalapril.

Methods

Patients

Nine patients, four male and five female, with uncomplicated essential hypertension were studied. Diagnostic work–up included rapid sequence urography in all patients, and renal angiography if considered appropriate. Age ranged from 36 to 54 years (median 44). Renal function was normal, as assessed by a GFR ≥90 ml/min/1.73 m^2 at entry. There were no signs of heart failure. Concomitant medication was not allowed. The patients gave informed consent. The study was approved by the ethical committee of the University Hospital.

Protocol

Previous medication had been withdrawn for at least four weeks before the study. Two weeks before the study the patients were instituted on a rigidly standardized diet, that is either 50 or 200 mmol sodium daily with standardized potassium (100 mmol) and fluid intake (2500 ml daily). Then the patients were hospitalized. After a run–in period of at least a week when blood pressure, sodium excretion and body weight were allowed to stabilize, renal function studies were performed. Thereafter enalapril (10 mg bid) was given for eight days. Renal function studies were repeated on the eighth day of treatment. Subsequently the medication was withdrawn. Patients were then crossed over to the other diet, and after a period of at least two weeks the whole study was repeated.

During the run–in as well as during the treatment period, 24-hour urine was collected continuously for determination of the excretion of sodium, potassium and creatinine. Cumulated

Table 1. Baseline values (mean ± SEM)

	Sodium 200 mmol	Sodium 50 mmol	% change	*P*
MAP, *mm Hg*	109 ± 2	110 ± 2	+1 ± 2	NS
GFR, *ml/min/1.73 m²*	111 ± 4	104 ± 4	−7 ± 2	<0.02
ERPF, *ml/min/1.73 m²*	431 ± 22	415 ± 27	−4 ± 3	<0.1
FF	0.261 ± 0.006	0.255 ± 0.010	+1 ± 3	NS
PRA, *nmolAI/l/hr*	1.0 ± 0.3	2.5 ± 0.8	+190 ± 59	<0.01
PAC, *nmol/liter*	0.44 ± 0.10	0.80 ± 0.16	+94 ± 19	<0.01
$U_{Na}V$, *mmol/24 hr*	201 ± 14	45 ± 7	−77 ± 6	<0.01
U_KV, *mmol/24 hr*	75 ± 5	75 ± 5	0 ± 0	NS
Serum Na, *mmol/liter*	142 ± 1	141 ± 1	−1 ± 1	NS
K, *mmol/liter*	4.3 ± 0.1	4.4 ± 0.1	+4 ± 4	NS
Body weight, *kg*	76.2 ± 3.6	75.2 ± 3.8	−1.4 ± 1.1	NS

Table 2. Responses to enalapril (mean ± SEM)

	Sodium 200 mmol	% change	*P*	Sodium 50 mmol	% change	*P*
MAP	98 ± 2	−10 ± 1	<0.01	94 ± 2	−15 ± 1	<0.01
GFR	112 ± 4	+1 ± 2	NS	110 ± 4	+6 ± 2	<0.02
ERPF	465 ± 25	+8 ± 2	<0.02	473 ± 30	+15 ± 4	<0.01
FF	0.243 ± 0.010	−7 ± 2	<0.02	0.236 ± 0.010	−7 ± 3	<0.02
PRA	6.5 ± 1.8	+487 ± 113	<0.01	14.3 ± 5.4	+513 ± 109	<0.01
PAC	0.40 ± 0.09	−6 ± 9	NS	0.77 ± 0.18	−9 ± 13	NS
$U_{Na}V$	212 ± 16	+2 ± 5	NS	49 ± 7	+4 ± 5	NS
serum Na	140 ± 1	0 ± 1	NS	140 ± 1	0 ± 1	NS
serum K	4.5 ± 0.2	+5 ± 2	NS	4.5 ± 0.2	+2 ± 3	NS
body weight	75.3 ± 3.3	−1.1 ± 0.2	<0.01	74.2 ± 3.3	−1.1 ± 0.7	<0.05

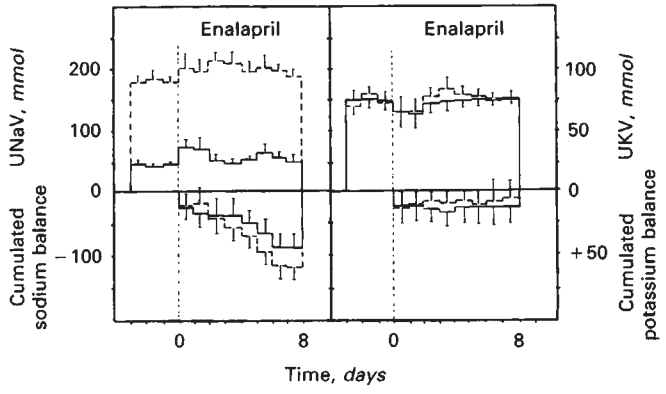

Fig. 1. *Effects of enalapril on the urinary excretions of sodium and potassium (upper panels) and on cumulated sodium- and potassium-balance (lower panels).* Data on low sodium intake are depicted by continuous lines, data on liberal sodium by broken lines. Data are presented as mean ± SEM.

sodium balance was calculated with the mean of the last three control days as baseline value. Blood pressure was measured four times daily with a non-invasive automatic device (Dinamap®) after 20 minutes of supine rest. The mean of these four readings is given in Table 1. Blood samples for the determination of plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were drawn after 20 minutes of supine rest and just before the morning dose of enalapril was given (8:00 a.m.). Body weight was measured daily (8:00 a.m.).

Treatment with enalapril resulted in an increase in sodium excretion on both sodium intakes (Fig. 1). This increase was already apparent on the first day of treatment in seven out of nine, and in five out of nine patients on low and liberal sodium, respectively. After one week of treatment sodium excretion matched intake again in all patients. By then the net sodium loss from the body was 105 ± 22 and 124 ± 18 mmol on low and liberal sodium, respectively (Fig. 1). The sodium loss was not significantly different for the different sodium intakes; for individual patients the sodium loss was virtually similar on both sodium intakes ($r = 0.77$, $P < 0.01$). The negative sodium balance was accompanied by a fall in body weight on both sodium intakes (Table 2). Potassium excretion tended to decrease somewhat with enalapril (Fig. 1), but the decrease did not reach statistical significance. Consequently, potassium balance did not change. The sum of the excretions of sodium and potassium, as an index of distal sodium delivery, increased in parallel with sodium excretion.

Methods

GFR and ERPF were measured simultaneously as the clearance of 125I-iothalamate and 131I-Hippuran [11], respectively. During the renal function studies the patients were in the supine position. After a priming dose was given, the radiopharmaceuticals were infused at a constant rate (Braun Unita II pump). After an equilibration period of 1.5 hour two 2-hour clearances were determined, each calculated from the 2-hour urinary tracer excretions and the mean serum tracer values from three samples drawn at the start, midway and the end of each

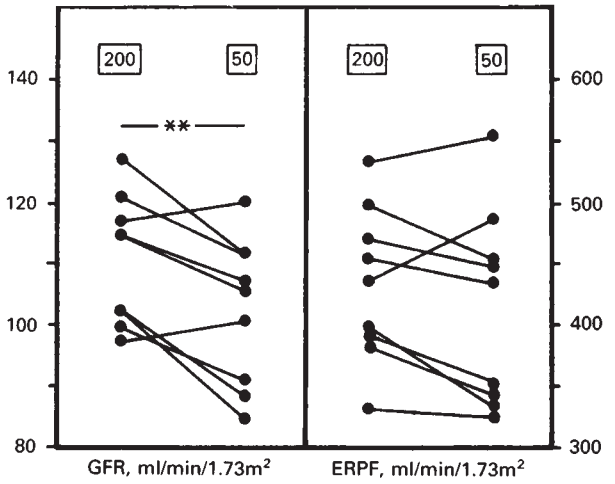

Fig. 2. *The individual values of GFR and ERPF on liberal (200 mmol) and low (50 mmol) sodium intake.* * $P < 0.02$.

two–hour period. The mean of the two clearances is given. During the procedure a diuresis of at least 200 ml/2 hr was maintained by oral administration of fluids. The coefficients of variation of the day–to–day determinations are 2.2 for GFR and 5% for ERPF, respectively [11].

PRA and PAC were measured by radio–immunoassay [12, 13]. Serum and urinary electrolytes were measured by standard auto-analyzer techniques.

Data are presented as mean ± SEM. Statistical evaluation was performed according to the Wilcoxon test for paired data, each patient being his own control. Results were considered statistically significant at a 5% level.

Results

Mean values for blood pressure and renal hemodynamics as well as hormonal parameters on both sodium intakes are given in Table 1. Blood pressure was similar on both sodium intakes. GFR was significantly lower on the low sodium diet. In seven out of nine patients ERPF also was lower on the sodium restricted diet (Fig. 2). Both PRA and PAC were higher on restricted sodium intake (Table 1).

Treatment with enalapril resulted in a fall in blood pressure on both sodium intakes (Table 2); the fall in blood pressure was more pronounced on the low sodium intake ($P < 0.02$).

The effects of enalapril on renal hemodynamics are shown in Figure 3. GFR increased during enalapril on the low sodium diet despite the fall in blood pressure. On liberal sodium intake however, no change was observed. Enalapril induced an increase in ERPF on both sodium intakes, the increase being more pronounced on the low sodium intake ($P < 0.02$). No relationship was found between the fall in mean arterial pressure after enalapril and the responses of GFR ($r = -0.27$ and -0.11 on low and liberal sodium, respectively) and ERPF ($r = -0.53$ and -0.22 on low and liberal sodium, respectively). Filtration fraction decreased similarly on both sodium intakes.

A sustained rise in PRA was observed after enalapril on either diet (Fig. 4). PAC decreased in all patients at the onset of treatment, with a gradual return to baseline values during the next days of treatment. The renal response to enalapril was not

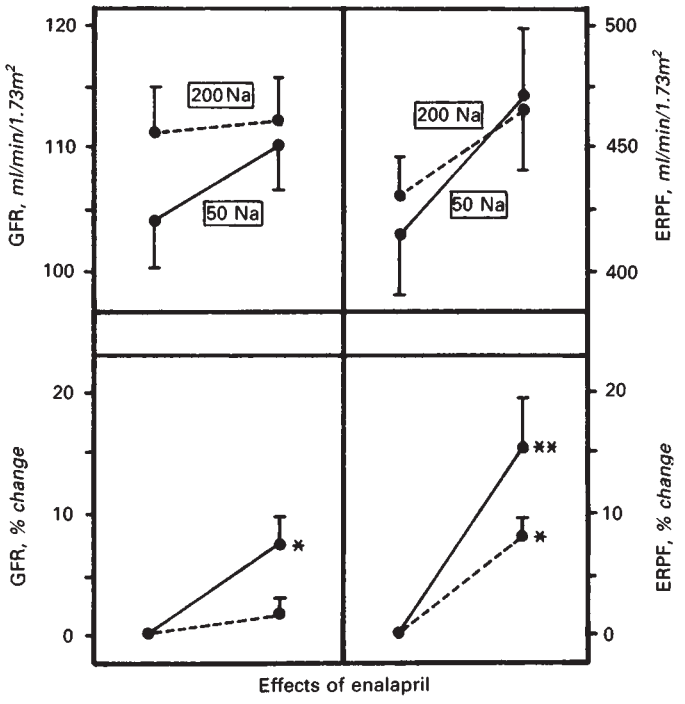

Fig. 3. *Effects of enalapril on GFR and ERPF on liberal (broken lines) and on low (continuous lines) sodium intake.* Data are given as absolute values (upper panel) and as percentage change (lower panel). Mean ± SEM. * $P < 0.01$.

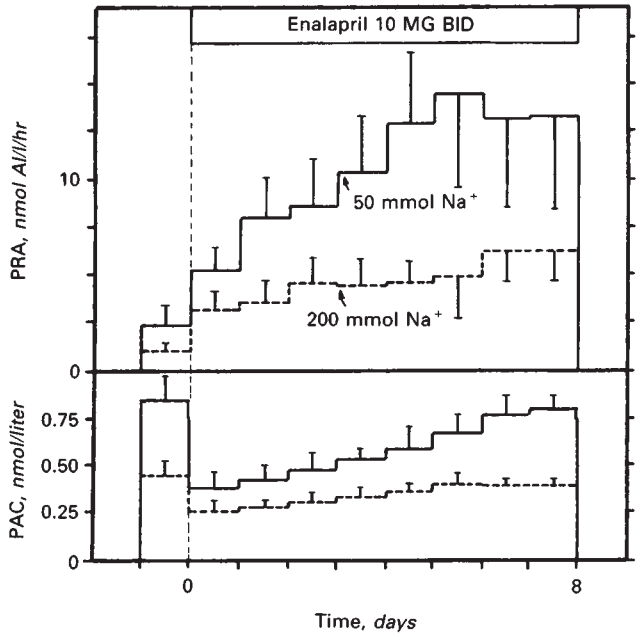

Fig. 4. *Effects of enalapril on PRA (upper panel) and PAC (lower panel), on low (continuous lines) and on liberal (broken lines) sodium intake.* Mean ± SEM.

correlated with either the log of initial PRA ($r = 0.18$ and 0.25 for GFR and $r = -0.45$ and -0.38 for ERPF on low and liberal sodium, respectively), or with the change in PRA on either diet

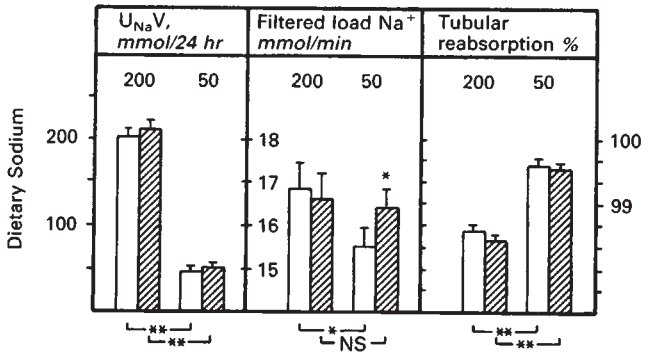

Fig. 5. *Twenty-four urinary sodium excretion (left panel), amount of sodium filtered (middle panel) and percentage of sodium reabsorbed (right panel) on both sodium intakes, without (open bars) and with (hatched bars) enalapril.* * $P < 0.02$, ** $P < 0.01$.

($r = 0.11$ and -0.09 for GFR and $r = 0.17$ and 0.23 for ERPF on low and liberal sodium, respectively).

The parameters of renal sodium handling in steady state, both with (measured at day 8; at that time sodium excretion matched intake again) and without enalapril, are given in Figure 5. It shows the urinary excretion of sodium, the total amount of sodium filtered at the glomerulus, and, calculated from these two, the percentage of sodium reabsorbed by the tubules.

Without enalapril, the lower sodium excretion on the 50 mmol sodium diet is due to both a fall in the filtered load of sodium ($P < 0.02$) and a rise in net tubular reabsorption ($P < 0.01$). During enalapril however, the situation is quite different. With enalapril the decrease in filtered load during sodium restricted diet is no longer apparent and the fall in urinary sodium excretion now only is accounted for by a rise in net tubular reabsorption ($P < 0.01$).

Discussion

The purpose of our study was to document the renal response to a moderate restriction of dietary sodium in essential hypertension and to establish the role of the RAAS in this response. We chose to study the 50 to 200 mmol range because 200 mmol approximates the habitual intake in our region, and indeed in a greater part of the western world, and 50 mmol is the sodium intake we recommend to our hypertensive patients.

It has long been known that a dietary restriction of sodium to less than 10 mmol/24 hr (that is, to less than 5% of the habitual intake) results in a decrease in GFR and ERPF in hypertensive patients [8] and in healthy individuals [3]. Our results show that a moderate restriction to approximately 25% of the habitual intake is already associated with a fall in GFR and, albeit less consistently, ERPF.

We observed an increase in sodium excretion after enalapril in all patients, resulting in a net sodium loss of approximately 100 mmol on either sodium intake. This amount of sodium is equivalent to approximately 0.75 liter of extracellular fluid, which is in accord with the weight loss we observed. The effects of enalapril on renal hemodynamics and sodium handling were studied after one week of treatment. At that time sodium excretion matched intake again, thus the patients were in a new sodium steady-state. Potassium excretion tended to decrease somewhat, but the decrease did not reach statistical significance.

The effects of enalapril on GFR and ERPF were significantly more pronounced on low sodium intake. This underlines once more the importance of sodium status when considering the effects of ACE-inhibition. It could be that a large part of the divergence in data dealing with the effects of ACE-inhibitors on GFR is accounted for by differences in the sodium status. Our findings are in accord with a variety of acute experiments in animals [6, 7] and man [5, 14] in which salt-loading blunted or abolished the increase in renal blood flow observed after ACE-inhibition or after an AII-antagonist. This has provided evidence that the RAAS, probably AII-mediated vasoconstriction, is involved in the renal hemodynamic response to sodium restriction [15]. Yet it has recently been called doubtful that the renal hemodynamic response is only accounted for by the RAAS in view of the quite pronounced changes in the renin-system as compared to the subtle changes in renal function [16].

This is the first study, to our knowledge, with the individual subjects as their own control, thus allowing a strict comparison of the responses to ACE-inhibition on the different sodium intakes. In our patients ACE-inhibition restored ERPF on the low sodium diet to precisely the level measured on the liberal sodium intake. Similarly, ACE-inhibition restored GFR on the low sodium diet to a level only insignificantly below that on liberal sodium. As a change in GFR is related to the change in ERPF as well as the change in blood pressure [17], the less precise match of GFR may be due to the somewhat more pronounced fall in blood pressure on low sodium intake. Our results are in good agreement with the abovementioned studies, and again provide evidence that the lower values of GFR and ERPF during low sodium intake are due to all AII-mediated renal vasoconstriction, although they do not rule out the possibility of a role for other hormonal systems.

The adaptation of renal sodium handling to sodium restriction was characterized by both a decrease in the amount of sodium filtered (mainly due to a decrease in GFR) and an increase in sodium reabsorbed (Fig. 5). This adaptation was altered by treatment with enalapril. With enalapril the difference in filtered load between low and liberal sodium was no longer apparent, whereas the difference in tubular reabsorption between low and liberal sodium intake was still present. This could mean that ACE-inhibition blunts the adaptation of GFR (and consequently the adaptation of filtered load) to altered sodium intake. This also suggests that tubular adaptive mechanisms are not affected, but our study design, only providing data on overall sodium reabsorption, does not allow support of this hypothesis.

Sodium loss induced by enalapril

The net sodium loss we found is consistent with our earlier findings with enalaprilic acid and with the findings of other investigators [18, 19]. The sodium loss can be expected to have influenced the absolute levels of both filtered load and tubular reabsorption after enalapril on either diet. As the sodium loss was similar on both diets however, the sodium loss is less likely to be involved in the phenomenon of blunting of the adaptation of filtered load to altered sodium intake.

Enalapril induced a sustained rise in PRA on both sodium intakes. Somewhat in contrast, PAC returned to baseline after an initial decrease on both sodium intakes. With regard to the

effect on PAC a few remarks should be made. First, the initial decrease in PAC could well have played a role in the sodium loss at the onset of treatment. Second, the return to baseline of PAC could be due to the sodium loss itself (which would imply that the axis sodium balance, renin–angiotensin–aldosterone is still functioning to some degree, despite ACE-inhibition), to subtle changes in potassium balance, or to non-AII or potassium–mediated mechanisms of aldosterone release, that is ACTH. In this respect it is of interest that in our patients the difference between both PRA and PAC on low and liberal sodium persisted under ACE-inhibition. This could suggest that this systemic (circulating) RAAS activity is still modified in response to sodium restriction, despite ACE-inhibition. As we did not measure AII levels, however, this evidence remains circumstantial.

Relevance of the blunted glomerular response to sodium restriction under ACE-inhibition

It could be that it impairs the capacity to maintain sodium homeostasis, as has been shown after captopril in rats subject to a much more pronounced sodium restriction [20]. Perhaps due to the less–severe sodium restriction in our patients, our study does not support this assumption. It could also be that, in interplay with the effects of ACE-inhibition on the systemic vascular bed, the blunting of the glomerular adaptive mechanisms contributes to the greater sodium sensitivity of blood pressure under ACE-inhibition.

In conclusion, an only moderate restriction of dietary sodium elicited a distinct response of renal hemodynamics in patients with essential hypertension. Both the amount of sodium filtered and tubular sodium handling appeared to be involved in the adaptation to sodium restriction. Treatment with ACE-inhibitor enalapril blunted the renal hemodynamic responses to sodium restriction. Therefore, these are likely to be mediated by angiotensin II.

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