Sodium intake and therapy resistance to ACE inhibition
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**Document Version**
Publisher's PDF, also known as Version of record

**Publication date:**
2005

**Link to publication in University of Groningen/UMCG research database**

*Citation for published version (APA):*

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Download date: 02-04-2020
Introduction

The hemodynamic response to altered sodium intake varies between subjects. Studies on the hemodynamic response to altered sodium intake usually focus on the effect of elevated sodium intake on blood pressure, i.e. the sodium sensitivity of blood pressure (1). Sodium sensitivity of blood pressure has been reported to be associated with increased cardiovascular and renal risk (2,3), possibly even independent of elevated blood pressure (4).

In hypertensive subjects with a sodium sensitive blood pressure, the renal hemodynamic response to elevated sodium intake has been reported to be abnormal (5). In sodium resistant hypertensive subjects, a rise in sodium intake induces a rise in renal plasma flow (ERPF) (5,6). This is in accord with data in small studies in normotensive subjects (7-13). In sodium sensitive hypertensive subjects, however, renal plasma flow decreases in response to high sodium (5,6,13), resulting in a rise in filtration fraction (FF) as the glomerular filtration rate (GFR) remains unchanged (6). This renal response is associated with a rise in urinary albumin excretion, which is a predictor for renal and cardiovascular risk (14-16). It has therefore been proposed that a decrease in renal plasma flow in response to high sodium intake is a marker of increased cardiovascular and renal risk.

Experimental studies suggest that subclinical, acquired, renal injury is involved as a causal mechanism underlying sodium sensitive hypertension (17). Accordingly, the abnormal renal response to high sodium in sodium sensitive hypertension might be a reflection of subclinical hypertensive renal damage. However, whether a decrease in renal plasma flow in response to high sodium intake is cause or consequence of sodium-sensitive hypertension is unknown. To explore this issue, we investigated the responses of renal hemodynamics and blood pressure to high sodium intake in normotensive volunteers, i.e. a population without prior renal exposure to elevated blood pressure, to exclude subclinical renal hypertensive damage as a causal factor.

Methods

Patients

Thirty-six normotensive male subjects (age 30 ± 13 years) were studied as described before (18) in balance on a low (50 mmol Na+/day) and a high (200 mmol Na+/day) sodium intake in randomized order. The subjects were on each diet for a week. For assessment of dietary compliance, 24-h urine samples were collected on day 4 and 6 after the start of diet. To proceed with the experiments, urinary sodium excretion had to be below 70 mmol/day for low sodium and above 170 mmol/day for high sodium.
Renal hemodynamic measurements

The experiments on day 7 after the start of the diet were as follows: having abstained from food, alcohol, and strenuous exercise for 12 h, subjects reported to the research unit at 8:00 a.m. During the experiments, they remained in semi-supine position except when voiding. An intravenous cannula was inserted into each forearm, for infusion of fluids and drawing of blood samples, respectively. To ensure sufficient urine output, glucose (5%, 250 ml/h) was administered in the right antecubital vein. After a run-in period from 8 am until 10 am, GFR and ERPF were measured as previously described, using constant infusion of 125I-iothalamate and 131I-Hippuran, respectively. (The day-to-day variation of GFR in this set-up is 2.2% and of ERPF 5% (19)). GFR and ERPF were corrected for standard body surface area (1.73m2) and FF is calculated as the ratio of GFR and ERPF and expressed as %. Mean arterial blood pressure (MAP) was measured at 15 minute intervals using a non-invasive device (Dinamap®; GE Medical systems, Milwaukee, WI) during the hemodynamic measurements.

Blood samples

All blood samples were drawn in pre-chilled tubes and centrifuged at 4° C. Plasma and serum was stored at -20° C until analysis. Serum and urinary values of sodium, potassium, urea and creatinine were measured by standard autoanalyzer technique (MEGA, Merck, Darmstadt, Germany). Plasma renin activity (PRA) was assessed by quantification of generated AngI with a RIA (Rianen AngI Ria Kit; Dupont, Wilmington, DE). Aldosterone levels were determined with a RIA as described before (20).

Data Analysis

Data was analyzed using SPSS 10.0 (SPSS inc. Chicago) and expressed as mean (SD). For blood levels, the averages of the values measured at 10:00a.m. and 12:00p.m. were used. For blood pressure, the average values over this period were used. Differences between high and low sodium status were tested using the Student’s t tests for paired data. Differences between the subgroups were tested using the unpaired Student’s t test. A two sided p-value of less than 0.05 was considered to be significant. To test for correlation between changes in MAP, ERPF and GFR, Spearman’s bivariate correlation was calculated.

Results

Mean group values are shown in Table 1. It shows a good dietary compliance as estimated from the urinary excretion of sodium, accompanied by the expected decrease in PRA and aldosterone on high sodium. Potassium excretion was similar on low and high sodium, with a slight increase in serum potassium on high sodium. Urea excretion was higher on high sodium. Blood
pressure was similar on low and high sodium (MAP: 0 ± 5%, ns). High sodium intake increased ERPF by 5 ± 10% (p<0.01) and GFR with 7 ± 9% (p<0.01), without a change in FF: 2 ± 9% (ns). The distribution of the changes in MAP, ERPF, GFR, and FF are shown in figure 1. In spite of the mean rise at group level, ERPF and GFR decreased in response to high sodium intake in eleven and eight out of the 36 subjects, respectively. Among these subjects, the drop in ERPF exceeded the day-to-day variability in six out of eleven, and in GFR in eight of eight subjects. The sodium sensitivity of blood pressure (% change in MAP) did not correlate with the % change in ERPF to increased sodium, as shown in figure 2A. The response of ERPF to increased dietary sodium correlated significantly with the response of GFR (R=0.49, p<0.01, figure 2B). However, the changes in GFR and ERPF were not proportional, as shown by the deviation of the regression line from the line of identity. This difference was statistically significant, as apparent from the linear regression equation, with a beta-coefficient of 0.45 (95%CI: 0.17-0.72) which was significantly different from 1, and an intercept of 4.8 (95%CI: 1.7-7.9) which was significantly different from 0 (p<0.05). As a consequence, FF increased in subjects in whom ERPF did not increase in response to high sodium.

Table 1 Group characteristics on a low and high salt intake (mean (SD))

<table>
<thead>
<tr>
<th></th>
<th>Low salt</th>
<th>High salt</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNaV (mmol/day)</td>
<td>50 (28)</td>
<td>236 (62)</td>
</tr>
<tr>
<td>UKV (mmol/day)</td>
<td>86 (23)</td>
<td>89 (30)</td>
</tr>
<tr>
<td>UUreumV (mmol/day)</td>
<td>320(93)</td>
<td>383 (108)</td>
</tr>
<tr>
<td>UCreatinineV (mmol/day)</td>
<td>15 (2.6)</td>
<td>15 (3.5)</td>
</tr>
<tr>
<td>Serum Na (mmol/L)</td>
<td>137 (2)</td>
<td>137 (2)</td>
</tr>
<tr>
<td>Serum K (mmol/L)</td>
<td>4.0 (0.32)</td>
<td>4.2 (0.32)</td>
</tr>
<tr>
<td>Serum Creatinine (umol/L)</td>
<td>91 (8.9)</td>
<td>90 (9.4)</td>
</tr>
<tr>
<td>PRA (nmol/L/h)</td>
<td>0.72 (0.64)</td>
<td>0.12 (0.13)</td>
</tr>
<tr>
<td>SerumAldosterone (nmol/L)</td>
<td>0.49 (25)</td>
<td>0.17 (0.08)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>89 (6)</td>
<td>89 (6)</td>
</tr>
<tr>
<td>ERPF (mL/min/1.75m2)</td>
<td>508 (85)</td>
<td>536 (101)</td>
</tr>
<tr>
<td>GFR (mL/min/1.73m2)</td>
<td>110 (12)</td>
<td>118 (14)</td>
</tr>
<tr>
<td>FF (%)</td>
<td>21.6 (2.2)</td>
<td>22.2 (2.8)</td>
</tr>
</tbody>
</table>

*p<0.05, #p<0.01 High vs Low sodium diet
To explore for differences between the subjects that might explain the responses of ERPF, we made a post-hoc comparison between two subgroups defined according to the response of ERPF being above or below the group median (i.e. above or below a 5% increase). Table 2 shows the clinical characteristics of the study population according to this break-up. No differences in urinary sodium, potassium or urea excretion were found between the groups, neither on low, nor on high sodium, nor were there any differences in the changes in these parameters elicited by the change in sodium intake. Serum electrolytes, creatinine, aldosterone and PRA, as well as blood pressure were also similar. The change in ERPF was different by definition. The change in GFR in response to high sodium was significantly lower.
in the subjects with change in ERPF below the median. Finally, in these subjects, a significant rise in FF occurred during high sodium, that was not encountered in the subjects with a change in ERPF above the median.

### Discussion

This is to the best of our knowledge the first study allowing analysis of individual renal hemodynamic responses to altered sodium intake in young normotensive subjects. Whereas prior studies reported on the renal hemodynamic changes during altered sodium status, these were invariably too small (i.e. 8-15 subjects) (7-13) to allow individual analysis. In accord with these studies, the shift from moderately restricted to a high sodium intake was associated with a rise in ERPF and GFR when assessed at group level. However, individual

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**Table 2: Subject characteristics by break-up according to median change in ERPF (mean (SD))**

<table>
<thead>
<tr>
<th></th>
<th>Change ERPF above median</th>
<th>Change ERPF below median</th>
<th>p-value $</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low salt</td>
<td>High salt</td>
<td>Low salt</td>
</tr>
<tr>
<td>UNaV (mmol/day)</td>
<td>49 (27)</td>
<td>241 (26)#</td>
<td>52 (30)</td>
</tr>
<tr>
<td>UKV (mmol/day)</td>
<td>87 (25)</td>
<td>91 (29)</td>
<td>85 (22)</td>
</tr>
<tr>
<td>UUreumV (mmol/day)</td>
<td>330 (96)</td>
<td>379 (112)*</td>
<td>310 (92)</td>
</tr>
<tr>
<td>UcreatinineV (mmol/day)</td>
<td>14 (2)</td>
<td>15 (4)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Serum Na (mmol/L)</td>
<td>136 (2)</td>
<td>136 (2)</td>
<td>137 (2)</td>
</tr>
<tr>
<td>Serum K (mmol/L)</td>
<td>4.0 (0.4)</td>
<td>4.2 (0.4)</td>
<td>4.0 (0.2)</td>
</tr>
<tr>
<td>Serum Creatinine (umol/L)</td>
<td>92 (9)</td>
<td>91 (10)</td>
<td>91 (10)</td>
</tr>
<tr>
<td>PRA (nmol/L/h)</td>
<td>0.83 (0.46)</td>
<td>0.24 (0.15)#</td>
<td>0.61 (0.77)</td>
</tr>
<tr>
<td>Serum Aldosterone (nmol/L)</td>
<td>0.48 (0.26)</td>
<td>0.16 (0.07)#</td>
<td>0.49 (0.24)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>89 (6)</td>
<td>90 (7)</td>
<td>89 (7)</td>
</tr>
<tr>
<td>ERPF (mL/min/1.73m2)</td>
<td>499 (80)</td>
<td>564 (99)#</td>
<td>518 (91)</td>
</tr>
<tr>
<td>GFR (mL/min/1.73m2)</td>
<td>109 (8)</td>
<td>121 (12)#</td>
<td>112 (16)</td>
</tr>
<tr>
<td>FF (%)</td>
<td>22.1 (2.6)</td>
<td>21.7 (2.8)</td>
<td>21.9 (1.9)</td>
</tr>
</tbody>
</table>

No difference between groups on High or Low sodium diet *p<0.05, #p<0.01 High vs Low sodium diet; $ difference in sodium induced change.
analysis shows that the range of the responses of ERPF and GFR to altered sodium intake was wide, with a decrease in ERPF during high sodium in a considerable proportion of this normotensive population. The change in ERPF was a determinant of the change in GFR but the responses of ERPF and GFR were not proportional. As a consequence, in subjects with a poor or absent rise in ERPF during increased sodium intake, FF increased in response to high sodium. Thus, an unfavorable renal hemodynamic response to high sodium occurs in a considerable proportion of a normal population in whom subclinical hypertensive renal damage is highly unlikely.

In our population the response of ERPF to altered sodium intake was not associated with the sodium sensitivity of blood pressure. This is at variance with prior studies in hypertensive subjects (5;6). Most likely, this discrepancy is explained by the fact that our population was normotensive. Moreover, the mean age in our population was 30 years, i.e. considerably lower than in the hypertensive populations reported in the literature, which hampers a too straightforward comparison. However, in a protocol similar to ours Chilero et al. did not find a relation between sodium sensitivity and change in ERPF in hypertensive patients either.

In discrepancies between studies on sodium sensitivity, differences in the assessment of sodium sensitivity, as well as confounding effects of changes in other dietary components should be considered. Our measurements were performed after one week on a standardized sodium intake after checking for dietary compliance and sodium balance by urinary sodium excretion and body weight, both three days and one day before the actual measurements. This allows a reasonably confident estimate sodium status, and of the achievement of sodium balance.

Our study was conducted as an outpatient study with strict dietary counseling. This set-up was chosen to minimize interference with the subjects’ normal activities and nutritional pattern. Dietary sodium restriction under outpatient conditions, however, can result in altered intake of other nutrients. In our study, high sodium intake was accompanied by an inadvertent increase in urea excretion, indicating a higher protein intake. The higher protein intake during high sodium may have affected renal hemodynamics, and have contributed to the higher mean ERPF and GFR during high sodium (21;22). However, the main finding of our study was presence of a decrease in ERPF during high sodium in a considerable part of our population. This phenomenon could not be explained by differences in protein intake, as supported by the similar urea excretion in subjects with a change in ERPF above as compared to below the median. The higher protein intake during high sodium, therefore, does not refute our conclusion.

Differences in potassium intake may be relevant as well. In a study in African Americans adding potassium (140 mmol/day) to a high sodium diet abolished the sodium induced rise in blood pressure in sodium sensitive hypertensive subjects (23). Potassium supplementation
Figure 2 Scatterplot, showing the association between the sodium induced change in Effective Renal Plasma Flow and Mean Arterial Pressure (A), and the sodium induced change in Effective Renal Plasma Flow and Glomerular Filtration Rate (B). The line of identity (dotted line in B) indicates values for unchanged Filtration Fraction.

decreased GFR and FF without affecting ERPF, which was unaffected by increased sodium intake. However, the impact of potassium may be less in Caucasian subjects like ours (24) and, as judged from urinary excretion, in our population potassium intake was similar during low and high sodium.

The range of sodium intake that we studied, from 50 to a 200 mmol, was chosen to represent a range that can be encountered in the normal population, rather than an unphysiologically wide range meant to unmask biological phenomena by forcing responses to the extreme. This approach increases the likelihood that the renal hemodynamic responses observed here have pathological and physiological relevance, although this assumption remains to be proven.

The assessment of the sodium sensitivity of blood pressure is considered to be cumbersome, even in a standardized setting in a specialized center (25). Moreover, data on the reproducibility of the renal response to altered sodium intake are lacking altogether. We have no data on the reproducibility of the renal response to sodium either, but the reproducibility or our renal function measurement is well-established. Even when the day-to-day variation of our measurement of 5% on ERPF (19) is taken into account, still a non-negligible proportion of our healthy subjects had a drop in ERPF during high sodium. We compared responses to increased sodium as a continuous variable to avoid arbitrary cut-offs.

Our population was relatively young, and may thus have included subjects that will develop hypertension at a later age. A propensity to develop hypertension can bear impact on renal hemodynamics long before a rise in blood pressure becomes manifest, as apparent from studies in normotensive offspring of hypertensive parents, who have lower renal plasma flow.
and higher filtration fraction compared to controls (26;27). However, the impact of sodium intake on renal hemodynamics in pre-hypertensive subjects has not been established, and as we have no information on the family history of our population, no further inferences can be made here. This is also true for other risk factors like albuminuria and lipid profile. However, it is unlikely that these would be of detectable relevance in a young population like ours. Longitudinal data would be needed to clarify whether the decrease in ERPF during high sodium in normotensive subjects is a marker for an increased long term cardiovascular and renal risk.

The mechanisms underlying the variance in the renal response to high sodium cannot be derived from our study. No differences in subject demographics, or in the adaptation of PRA and aldosterone to altered sodium intake were detected. The renal response to sodium can be affected by various pathophysiological factors, such as presence of diabetes (28;29), or presence of the non-modulating trait in hypertension (30). Prior studies from our group suggest that, in hypertensive subjects, a renal vasoconstrictor response to high sodium reflects inappropriate activity of the intrarenal - but not circulating - renin-angiotensin system during high sodium (12). Further studies, using blockade of the renin-angiotensin system, would be needed to investigate whether similar mechanisms might be operative in some normotensive subjects.

**Conclusion**

In young normotensive subjects, the range of the renal responses to high sodium is wide, and includes a drop in ERPF in a non-negligible proportion of the subjects. This renal response is not associated with sodium sensitivity of blood pressure. As this decrease in ERPF occurs in normotensive subjects it cannot be attributed to subclinical hypertensive renal damage. Longitudinal data are needed to explore the prognostic impact of the renal hemodynamic response to high sodium for long term cardiovascular and renal risk in normotensive subjects.
REFERENCE LIST


