Evaluation of a Rapid Protocol for the Assessment of Salt Sensitivity Against the Blood Pressure Response to Dietary Sodium Chloride Restriction

Ferruccio Galletti, Ida Ferrara, Francesco Stinga, Roberto Iacone, Francesco Noviello, and Pasquale Strazzullo

The "gold standard" for the assessment of salt sensitivity of hypertension is the blood pressure response to dietary NaCl restriction; nevertheless, for practical purposes, a more rapid test that would not depend on the patient's compliance to the dietary prescription would be very useful in clinical research and medical practice. The aim of this study was thus to evaluate the effectiveness and reliability of a rapid, easy-to-standardize protocol for the assessment of salt sensitivity against the blood pressure response to dietary salt restriction. A total of 108 hypertensive patients were screened for salt sensitivity by the modified protocol of Grim et al. Thereafter, nine patients identified by the test as salt sensitive and nine identified as salt resistant followed, for two consecutive periods of 1 week, a diet with normal (200 mmol/day) or low (50 mmol/day) NaCl content. Compliance to the diet was checked by repeated 24-h urine collections. The group as a whole experienced a significant fall in blood pressure during the low Na diet (mean pressure = 123 ± 3 v 118 ± 3 mm Hg; P < .05). However, whereas patients identified as salt sensitive by the Grim protocol had a marked and significant blood pressure decrease (systolic -12 mm Hg, diastolic -7 mm Hg), no change was observed in those classified as salt resistant (systolic -2 mm Hg, diastolic -2 mm Hg). A significant correlation between changes in urinary Na excretion and changes in blood pressure was found only in salt-sensitive hypertensive patients. In conclusion, the modified Grim protocol tested in this study was able to correctly predict a significant blood pressure response to dietary salt restriction in the majority of cases. A validation of this test in a larger patient population may be advisable.

KEY WORDS: Hypertension, blood pressure, sodium, salt sensitivity, salt, diet.

Dietary salt restriction generates a heterogeneous blood pressure (BP) response in both normotensive subjects and patients with essential hypertension. In practice, however, the classification of an individual patient as sensitive or resistant to salt restriction is made difficult by several factors, including the patient's adherence to the dietary prescription, the relatively long time required to obtain a reliable response, and the limited value of a single clinic (or office) blood pressure measurement to assess this response with reasonable accuracy. These obstacles could be overcome if a rapid, easy-to-perform, and standardized test were available for use in clinical research and medical practice.

Among several methods previously used in the literature, we focused on the test originally proposed...
by Grim and coworkers as one deserving special attention, as it was able to consistently identify subjects with defined characteristics (low renin activity, more advanced age, overweight) as salt sensitive as compared with salt resistant individuals. For this reason, we decided to evaluate the ability of this test to correctly identify salt-sensitive versus salt-resistant hypertensive patients in comparison with the standard reference procedure of dietary NaCl restriction.

METHODS

Patients The study population was made of mild or moderate essential hypertensive patients consecutively referred to the Outpatient Clinic at our institution. Inclusion criteria were: diastolic blood pressure (DBP) >95 mm Hg on three consecutive visits, age between 20 and 65 years, and body mass index (BMI) below 30 kg/m². Patients with diabetes mellitus, congestive heart failure, ischemic cardiac or cerebrovascular disease, plasma creatinine greater than 140 μmol/L, or premenopausal status were not considered for the study. A total of 108 patients were enrolled, and were asked to interrupt any treatment for at least 2 weeks (4 weeks if on diuretics) before entering the study. At the end of this run-in period, they were prescribed a standard 200 mmol/day sodium diet for 3 days and were then hospitalized for four days to be screened for NaCl sensitivity by the rapid protocol of Grim and coworkers with minor modifications. The research protocol was approved by the local ethical committee and all participants gave their informed consent to the study.

NaCl Sensitivity Test On the first day of hospitalization the patients were still kept on a 200 mmol/day Na diet. On the second hospital day, a NaCl load was given between 8 AM and noon as an intravenous infusion of 2 L of normal saline, at the constant rate of 500 mL/h. At the end of the NaCl infusion, blood pressure was measured in the supine position using an automated sphygmomanometer (Sentron Bard Biomedical, Lombard, IL) every 3 min for 30 min, and the mean of the last five measurements was used for the analysis. The next day, an acute NaCl depletion was induced by switching the patients to a 10 mmol Na/day diet and by administering three oral doses of 37.5 mg frusemide at 8 AM, 2 PM, and 8 PM. On this day, the participants were asked to drink 25 mL of water per kg body weight. On the fourth hospital day, blood pressure was measured at 8 AM with the same protocol described above, and the patient was then discharged. The NaCl sensitivity was defined as the difference between the mean blood pressure value found at the end of the NaCl load and the one measured at the end of the NaCl depletion maneuver. Body weight was determined every morning on a beam balance scale with the patient wearing light indoor clothing and no shoes.

Dietary Study A dietary protocol was followed by 18 patients previously screened for salt sensitivity by the above-described rapid procedure, and identified as salt sensitive or salt resistant based on the criteria described below (see Results). The protocol included two consecutive dietary periods of 1 week each with either normal (200 mmol/day) or low (50 mmol/day) dietary NaCl content and a constant potassium intake of 50 ± 70 mmol/day. Blood pressure and body weight were measured as described for the rapid protocol on the last day of each dietary period.

Biochemical Measurements Twenty-four-hour urine collections were obtained to determine urine volume and sodium excretion at baseline, on the days of the NaCl load and depletion procedure and during the two dietary periods. Urinary sodium was assayed by an ion selective electrode using a Beckman (Fullerton, CA) EA-2 Electrolyte Analyzer. Plasma renin activity (PRA) was measured by radioimmunoassay using a commercially available kit (Renin Kit, Technogenetics, Milan, Italy) in a subgroup of patients (n = 53) during the rapid study at the end of the NaCl load and contraction maneuver. It was again measured during the dietary study in all patients at the end of the high and low sodium regimens.

Statistics Statistical analysis was performed using the Statistical Package for the Social Sciences. The Kolmogorov-Smirnov test was used to analyze the characteristics of the distribution of the blood pressure response to the rapid test. One-way ANOVA was used to compare the characteristics of the groups. A paired, two-tailed Student's t test was used to compare the blood pressure response to dietary salt restriction in salt sensitive and salt resistant patients. Data are expressed as mean ± SEM.

Calculations Calculations were as follows: Mean blood pressure (MBP) = 1/3 [(systolic − diastolic blood pressure)/3] + diastolic blood pressure. Body mass index = weight (kg)/height (m²). NaCl-sensitivity, based on the rapid test, was the mean blood pressure value reached at the end of the NaCl load minus mean blood pressure measured after the NaCl depletion maneuver. NaCl-sensitivity, based on the response to dietary salt restriction, was the mean blood pressure obtained at the end of the high NaCl diet minus mean blood pressure measured after NaCl restriction.

RESULTS

NaCl sensitivity, as estimated with the modified Grim protocol, was normally distributed (Kolmogorov-Smirnov's test: z = 0.518). This allowed us to divide the study population by tertiles of NaCl sensitivity in patients with low (LS), moderate (MS), or high (HS) sensitivity. Table 1 reports the characteristics of the
three groups at the end of the run-in period. Patients in the high NaCl sensitivity group were slightly older and had higher systolic blood pressure than those with low NaCl sensitivity. The three groups had similar body mass index and also similar 24-h urinary sodium excretion at baseline, after the three days on a 200 mmol Na diet (HS: 193 ± 11; MS: 189 ± 15; LS: 190 ± 10 mmol / 24 h). Also during the salt-sensitivity test the three groups showed similar 24 h Na excretion (NaCl load in HS: 360 ± 19, MS: 349 ± 13, LS: 384 ± 20; NaCl depletion in HS: 237 ± 16, MS: 264 ± 14, and LS: 284 ± 14). There was an inverse relationship between salt sensitivity and PRA at all times in the study (after the intravenous NaCl load in LS group (n = 23): PRA 0.82 ± 0.16 ng/mL/h; MS (n = 13): 0.66 ± 0.09; HS (n = 17): 0.43 ± 0.07; after NaCl depletion, LS: 2.32 ± 0.38; MS: 1.54 ± 0.39; HS: 0.86 ± 0.20; P < .02 LS v HS). After the NaCl depletion maneuver, the HS group had a much smaller rise in their PRA than did the other two groups.

Nine consecutive patients from the upper tertile of salt sensitivity (HS) and nine patients from the lowest tertile (LS) were recruited for the dietary study. The characteristics of the two subgroups are given in Table 2; the two subgroups were similar to those from which they were drawn. Salt-sensitive patients were older and had higher blood pressure than salt resistant patients. PRA was higher in the LS as compared with the HS group on both high sodium (1.92 ± 0.24 v 1.11 ± 0.34) and low sodium diet (2.42 ± 0.20 v 1.50 ± 0.46; P < .05 between diets and LS v HS); whereas no differences were noted in the basal 24-h urinary Na excretion between the two groups (LS: 236 ± 22; HS: 221 ± 23).

One patient in the LS group was excluded from the dietary study because of his poor compliance with the low Na diet (24-h urinary Na excretion = 170 mmol / day). Without including this patient, compliance with the prescribed dietary sodium intake was quite satisfactory during the study; 24-h urinary Na excretion fell from 203 ± 16 and 214 ± 19 mmol/day to 85 ± 10 and 61 ± 7 in LS and HS group, respectively.

HS patients had a significant drop in MBP, evaluated either as absolute or percent fall of blood pressure, after low Na diet (absolute value = -9 ± 3 mm Hg, percent fall of blood pressure = -7 ± 2%, P < .05 v high Na diet). A significant drop during the low Na diet was also observed for both systolic (172 ± 5 v 160 ± 6 mm Hg) and diastolic blood pressure after low Na diet (108 ± 3 v 98 ± 3 mm Hg); whereas no significant change was observed in any blood pressure of LS subjects (absolute value = -2 ± 1 mm Hg; percentage = -1 ± 1%; systolic = 150 ± 7 v 148 ± 5 mm Hg; diastolic = 99 ± 4 v 98 ± 3 mm Hg).

As shown in Figure 1, all but two HS patients had a fall in mean blood pressure of at least 5 mm Hg during low Na diet; by contrast, in the LS group, only 2 patients attained a blood pressure fall of more than 5

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**Table 1. Characteristics of Study Population by Tertile of Salt Sensitivity**

<table>
<thead>
<tr>
<th></th>
<th>Low Na-Sensitivity</th>
<th>Moderate Na-Sensitivity</th>
<th>High Na-Sensitivity</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>45 ± 1</td>
<td>48 ± 1</td>
<td>50 ± 1*</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>153 ± 2</td>
<td>160 ± 3</td>
<td>168 ± 2*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>98 ± 1</td>
<td>102 ± 2</td>
<td>103 ± 2</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.9 ± 0.4</td>
<td>27.4 ± 0.3</td>
<td>27.5 ± 0.2</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>93 ± 3</td>
<td>96 ± 2</td>
<td>92 ± 2</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>2.73 ± 5</td>
<td>197 ± 6</td>
<td>200 ± 5</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>115 ± 10</td>
<td>112 ± 12</td>
<td>116 ± 11</td>
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</tbody>
</table>

* P < .05 versus low Na sensitivity. Mean ± SEM.

**Table 2. Characteristics of the Two Subgroups Participating in the Dietary Study**

<table>
<thead>
<tr>
<th></th>
<th>Low NaCl Sensitivity</th>
<th>High NaCl Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>High Na</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46 ± 2</td>
<td>—</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79 ± 3</td>
<td>79 ± 3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.3 ± 0.5</td>
<td>—</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>145 ± 3</td>
<td>151 ± 6</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>96 ± 2</td>
<td>99 ± 3</td>
</tr>
</tbody>
</table>

* P < .01 v low NaCl sensitivity; † P < .01 v high Na diet.
A significant, direct correlation was observed between individual changes in 24-h sodium excretion, upon shifting from high to low sodium diet, and corresponding changes in mean blood pressure for the HS subgroup ($r = 0.69, P < .01$); no such correlation was found for the LS group ($r = -0.06$) (Figure 2).

DISCUSSION

Although a large number of studies have addressed the question of salt sensitivity of blood pressure using different protocols, very few have attempted to validate any such protocol against the blood pressure response to dietary salt restriction. Studies by Weinberger et al. and Sharma et al. detected a significant correlation between the blood pressure response to a rapid test of salt sensitivity and the "fine" salt sensitivity assessed by the blood pressure response to a period of NaCl restriction. The main differences between these two studies and our present work are twofold. Both Weinberger et al. and Sharma et al. used arbitrary cut-off points to distinguish salt-sensitive from salt-resistant subjects in their studies. At variance with this criteria, as we have previously reported, we have proposed to apply the Gaussian distribution of the blood pressure response to the Grim modified test of salt sensitivity to identify as the most "salt-sensitive" patients those whose response fell in the upper tertile of the distribution, and as relatively "salt-resistant" those with a blood pressure response falling in the lowest tertile. This, we believe, is a more objective criterion.

The second difference is more substantial, in that Sharma's series consisted of normotensive subjects and Weinberger's population included both normotensives and hypertensives, whereas our study concerned solely hypertensive patients.

It was hypothesized that obesity and, consequently, insulin resistance, could be related to salt sensitivity of blood pressure; to avoid these confounding factors obese subjects were excluded from the study.

Thus, after the exclusion of obese subjects, NaCl sensitivity seems less related to body weight; in fact, in this study, the three groups with different salt sensitivity showed similar BMI.

Consistent with previous findings, the patients classified in the highest tertile of salt sensitivity by the rapid test in this study were slightly older and had somewhat higher blood pressure and significantly lower PRA as compared with subjects in the lowest tertile.

When the two subgroups of patients underwent a protocol of dietary NaCl restriction, a significant average blood pressure fall was achieved only by those classified as salt sensitive. Indeed, a clinically meaningful reduction in blood pressure was attained by only 2 of 8 patients classified as "salt resistant" by the rapid test, versus 6 of 9 in the "salt sensitive" subgroup. Although our patients' population was too small to enable us to determine reasonably reliable indices of sensitivity and specificity, these data speak in favor of a reasonably good agreement between the two procedures compared, and indicate a good potential for use of the rapid test for the screening of salt sensitivity in hypertensive populations. This conclusion is further supported by the observation that a very good correlation between the degree of dietary salt restriction achieved by individual patients and their respective reductions in blood pressure was detected only in the subgroup of patients identified as "salt sensitive" by the rapid test, whereas a negative, although not significant, association was found in the "salt-resistant" subgroup. In other words, the blood pressure response of "salt-sensitive" patients decreased in proportion to the extent that they reduced their sodium intake; by contrast, even substantial salt restriction was not associated with a blood pressure decrease in the subjects who were found to be "salt resistant" by the screening test.
We believe that the findings of the present study strongly argue for the pathophysiologic and clinical soundness of the concept of salt sensitivity, and for the potential usefulness of a rapid screening test with good sensitivity and specificity.

REFERENCES


